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CITY OF **VANCOUVER**

ADMINISTRATIVE REPORT

Report Date:	September 21, 2007
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Meeting Date:	October 2, 2007

TO: Vancouver City Council

FROM: Drug Policy Coordinator

SUBJECT: Drug Substitution and Maintenance Treatment

INFORMATION

The General Manager/City Manager submits this report for INFORMATION.

COUNCIL POLICY

In March of 2006 the Drug Policy Program outlined the importance of expanding drug substitution programs, including methadone maintenance and heroin-assisted treatment, and initiating research in the area of substitution and maintenance programs for stimulant users.

On December 14, 2006 Council approved Project Civil City which included the goals to reduce homelessness and reduce the open drug market by 50 percent.

On February **27,** 2007 Council moved the following motion: **THEREFORE BE IT RESOLVED THAT** Council direct the City of Vancouver Drug Policy Coordinator to prepare a report for Council that includes:

1. Examples of substitute treatment programs including their benefits and challenges;
2. The relationship between substitution treatment and crime and disorder; and
3. An update on the NAOMI project and the challenges that the project has faced including the attraction of sufficient number of participants;

In addition, on June 14th, 2007 Council requested staff to report back on the Inner Change Society's Chronic Addiction Substitution Treatment program (CAST) and how the program would be incorporated into the City's drug policy.

SUMMARY AND PURPOSE

The purpose of this report is to provide an overview of the status of current local and international substitution treatment programs and research for opiates and stimulants. This report gives examples of programs and practice, as well as various studies and trials underway, to test the efficacy of substitution treatment. An update on the North American Opiate Medication Initiative (NAOMI) is included. The benefits and challenges of the programs, and the findings and conclusions of the research put forward, include outcomes such as impact on crime, homelessness, public nuisance and social integration. Where data is available, the report provides information on cost effectiveness. A fuller body of information on all research presented in this report is available in Appendices 1 and 2. The report will also provide Council with information on the Inner Change Society's Chronic Addiction Substitution program and how this program relates to the City's Four Pillar Drug Strategy.

BACKGROUND

Substitution treatment is an important component of any comprehensive approach to addiction treatment. Drug substitution and maintenance treatment approaches involving the use of methadone and nicotine replacement have been around for a long time and have a considerable body of research indicating the important role that these kinds of therapies play in reducing harm from drug addiction. This kind of treatment focuses on replacing a harmful, and often illegal, addictive drug with a safer, legal, prescription drug within a regime of patient care under the supervision of a medical professional. Its objectives include: stabilizing patients until they are ready to be abstinent; reducing their dependence on the black market, with all its associated harms; reducing criminal activity; preventing blood-borne disease transmission and overdose deaths; and improving patients' personal, social and family relations. British Columbia has traditionally been a leader in developing drug maintenance programs and has one of the most comprehensive methadone programs in Canada. In fact in 1963 Dr. Robert Halliday initiated in British Columbia what is regarded as the first methadone program in the world. In recent years there have been numerous calls for expansion of the methadone program, the implementation of other available substitution therapies and more research in the areas of opiate and stimulant substitution.

DISCUSSION

There is a significant body of research on substitution treatment programs for those using illegal opiates; there is a much smaller but growing body of research on substitution treatment for stimulant users. In the case of opiate substitution, methadone is the most widely practiced and licensed treatment, followed by buprenorphine which is available in several countries in Europe. Heroin Assisted Treatment (HAT) has a recent history and is demonstrating good outcomes for recalcitrant dependent users. In the case of stimulant substitution, despite a growing body of research with several substitution drugs, no one single treatment has proven to be effective for cocaine and amphetamine dependent use but initial research has shown promising results for some populations.

Discussed below are the benefits and challenges associated with the different types of treatment available, or on trial, for both opiate and stimulant substitution with a primary focus on HAT for opiate substitution and some prominent interventions for stimulant substitution.

(For detailed information on all the topics discussed below, please refer to Appendix 1. For a comprehensive at-a-glance version, see Appendix 2).

Opiate Replacement Therapy

Methadone and Buprenorphine

Methadone maintenance therapy (MMT) is the most widely researched and practiced treatment for opiate dependence. Since it was first used for this purpose in the 1960s, it has been clinically tested through several studies and rigorous randomized control trials. It has a longer half life[1] than heroin (24-36 hours compared to two to three hours for heroin) which means it does not need to be administered as frequently as heroin, only once daily. Thus a patient could take part in a normal day's activities that may include rehabilitation, family life, a job, etc. without going through withdrawal. Its effectiveness, safety, cost-efficiency and ability to reduce illegal drug use and promote positive health outcomes is firmly established. Results from studies on methadone indicate that it helps the patient in

- reducing illicit opioid use
- reducing sharing of injection equipment
- reducing criminality
- increasing likelihood of full employment and
- introducing positive lifestyle changes

In Vancouver, 76 licensed pharmacies provide methadone maintenance treatment to a total of 2,729 patients.

Buprenorphine is available in several countries in Europe: France, Denmark, Austria, Finland, Luxemburg and the U.K. It has been licensed since 2002 in the US and recently in Canada. Although not as extensively studied as methadone, it has been investigated for its efficacy as an opioid replacement therapy and provides evidence of good societal outcomes. In addition, it has an advantage over methadone, in that it has a longer half-life than methadone and so can be dispensed less frequently i.e. every other day.

Although both methadone and buprenorphine are used effectively in the treatment of heroin dependence, retention rates in treatment and suppression of illegal use are better with appropriate doses of MMT. It is also cheaper than Buprenorphine.

According to a World Health Organization (WHO) report, since approximately 10% of an estimated 12.6 million Intravenous Drug Users (IDU) in the world are HIV-positive as a result of injection drug use, the availability of substitute maintenance treatment providing safe alternatives is imperative. Thus, both methadone and buprenorphine have recently been included in the WHO list of essential medicines. However, despite the benefits and reputation of buprenorphine and MMT and, in the latter case, a large body of evidence, these replacement therapies are not effective or desirable for a small minority of severely dependent patients who are unable or unwilling to respond to the available treatment. For

[1] Half life is the time it takes for a drug's concentration in the body to be reduced by one half. In essence, it refers to the duration of a drug's action

this group, retention is limited and there is a continued use of street drugs. Many of these treatment-resistant, heroin-dependent users, typically, are severely marginalized, have a high rate of HIV prevalence and overdose, and are involved in high risk activities like needle sharing and unsafe sex. To address this population some European jurisdictions have implemented Heroin Assisted Treatment (HAT) programs in an attempt to enroll a larger percentage of the population heroin users into treatment programs than is currently reached with methadone and buprenorphine.

Prescription of pharmaceutical heroin

Over the last decade, several studies and trials have been conducted to test the efficacy of pharmaceutical heroin for treating the most recalcitrant heroin users. Four countries (Switzerland, Netherlands Germany and Spain) have successfully conducted studies on its efficacy and drawn conclusions; the UK and Canada are in the process of conducting heroin trials and awaiting results and Belgium is scheduled to start trials soon.

Switzerland
In Switzerland, the results of HAT tested in a 1994 National Cohort Study (n=1969 at 21 sites) showed excellent outcomes for patients, in terms of retention rates, crime reduction, social integration and overall health. Consequently, on March 8, 1999, the Federal Council authorized HAT throughout Switzerland, thus firmly establishing it as part of its treatment pillar. Patient numbers have steadily increased over the years: from less than 800 in 1998, in 2005 there were a total of 1,428 clients undergoing HAT in 21 outpatient centres and two prisons. HAT enrolment makes up about 5% of all Swiss heroin users in treatment.

Further benefits of the Swiss experiment are highlighted through a study of the trends of heroin use incidence in Zurich before, during and after the heroin epidemic. In 1975, 80 new users were recorded, which increased to 850 in 1990 and declined to 150 in 2002. The authors concluded that the medicalization of heroin –through HAT and MMT-- made it less attractive to young people, which, in turn, contributed to the decline in the population of problematic heroin users as compared with other countries. This research also indicated that allegations from some quarters that the Swiss so-called "liberal drug policy" would attract new users and lengthen the addiction of the existing users were indeed false.

One criticism leveled against the Swiss heroin trial was that it was inconclusive, because it was just an observational study and not a randomized control trial, which is considered to be the strongest possible form of research. However, a WHO panel of experts supported the conclusions of the study. Moreover, a small randomized control trial (n=51) which formed part of the large observational study and in which two groups were randomized - the control group with MMT and the treatment group with HAT and MMT - showed superior results for the latter.

In spite of the challenge, the Swiss Federal Government considered the evidence from the study, the recommendations from experts, and the push from an overwhelmingly favourable public opinion to legislate HAT as part of treatment.

Results of HAT as recorded in 1999 included the following:
Crime

- Income from illegal activity (determined by police records and individual testimony)decreased from 70% to 10%

- Offenders and offences decreased by about 60%
- Shoplifting decreased from 35% to 16.1%
- Breaking and entering decreased from 6.9% to 0%

Social Integration

- Homelessness went down from 12% to 1%
- Unstable housing rate fell from 43% to 21%
- Employment rates grew from 14% to 32%
- Debts during the treatment period were substantially reduced
- Patients' contact with the drug scene fell from 29% to 2%

Cost Effectiveness

- Savings in criminal investigation, prison days and health improvements
- Net economic benefit of $40 (45 Fr) per patient-day (approximately $15,000 Cdn per person per year)

Other

- From the 200 persons leaving the program per year, approximately 50 patients switched to abstinent-based treatments while almost 90 switched to methadone.
- General health improved; marked decrease in injection-related skin diseases
- Illicit heroin and cocaine use decreased rapidly (Uchtenhagen, 1999)

Netherlands

In the Netherlands, despite a comprehensive network of treatment and harm-reduction services, approximately one-fourth of MMT patients tend to use illegal heroin and have attendant problems of mental and physical health, social exclusion and crime. In a search for alternative substitution therapy, between 1998 and 2001, two randomized control trials were conducted with a total of 549 patients in six cities to determine whether supervised medical prescription of pharmaceutical heroin could successfully treat MMT-resistant users. The interventions consisted of injectable or inhalable pharmaceutical heroin plus methadone, compared with methadone alone. Throughout the treatment, psychosocial support was made available.

Results established that supervised medical prescription of heroin was safe and it improved participants' physical, mental and social functioning. Results also indicated a good adherence rate to treatment and found that heroin plus methadone was significantly more effective than methadone alone. Economically, co-prescription of heroin in the case of chronic treatment-resistant heroin-dependent users was more cost effective, compared with treatment with methadone alone, with average savings of $19,000 Cdn per patient per year. There was also a reduction in the crime rates in the HAT group.

Germany

Two clinical trials engaging 1032 participants over three years were recently carried out to determine if the prescription of pharmaceutical grade heroin is more effective than MMT in stabilizing refractory clients. It is also seeking to ascertain (through a second trial) whether medically prescribed heroin over a longer term can enhance the improvements made in the first study, focusing on outcome parameters such as reduction of illicit drug use, mental and social well being, overcoming addiction and integration into addiction services.

Results showed that, overall, the heroin group had fared better than the control methadone group: higher retention rates, improvement in physical and mental health, decline in street heroin use, decline in cocaine use, and decline in high-risk behaviour (such as needle sharing). The German trials established that in the case of treatment-resistant heroin users, heroin prescription was found to be superior in a statistically significant way over methadone

treatment. In terms of its relationship to crime and disorder, there was an increase in employment rates and a marked decline in criminal behaviour e.g. illegal income generation.

Spain
Similarly, Spain's recent trials found that the HAT group fared better in terms of physical health, risk behaviour for HIV and reduced drug-related problems and street heroin use than the MMT group. It concluded that pharmaceutical heroin could be safely delivered in the local context and was more effective together with methadone than methadone alone, for the treatment of recalcitrant, socially marginalised, severely addicted and physically and mentally affected opioid patients.

UK
The UK has a unique history of prescribing opiates (and stimulants) for addiction treatment. In 1926 a Home Office report established the doctor's right to prescribe heroin. Over the following three decades that this practice continued, there was no evidence to suggest that heroin prescription led to an increase in the number of heroin-dependent users. The situation changed, however, in the 1960s when heroin prescribed by some GPs was found to be leaking into the burgeoning black market. Concerns regarding this situation led to some significant changes: heroin could now be prescribed only by those doctors holding a special license and doctors were obligated to notify the healthcare system of the number of dependent users treated. It was also recommended that special outpatient clinics should be set up for the purpose of prescribing heroin. The rationale was that such clinics would decrease drug crimes (by providing heroin to the user), reduce harm to the user (by maintaining heroin purity), and deter black marketing by bringing heroin under tighter control. The clinics provided prescription heroin and, in some cases, injectable methadone. Gradually, this gave way to injectable and ingestible methadone, the main rationale for this being that methadone reduces the need to inject frequently. In the mid 1970s, there was a dramatic rise in the prescription of injectable methadone which led to a drop in heroin being prescribed and, eventually, oral methadone surpassed both as the preferred treatment.

In an effort to reduce crime, and encouraged by evidence from Switzerland and the Netherlands, the UK's National Health Service has embarked upon three trials with 150 chronic heroin-dependent users. Results will be announced in July 2008. Typically, a heroin-dependent user in the UK needs $34,000 Cdn/year to fund his or her heroin addiction and incurs costs of $100,000 Cdn/year in crime. It is estimated that 60% of crime is drug related; this would decline significantly as a result of heroin prescription. Currently, heroin maintenance is estimated to cost $27,000 Cdn per person. Economic savings from crime reduction, it is expected, would far outweigh the cost of heroin maintenance.

Canada
About 60,000-90,000 people are estimated to be addicted to heroin in Canada. As in other countries, they face the risks of lethal overdoses, exposure to HIV and Hepatitis C and tend to be involved in drug-related violence and crime. A recent Canadian study estimated the overall social costs of substance use in Canada at $39.8 billion for 2002. While a majority of these costs stem from the use of alcohol and tobacco, some 20% (or $8.2 billion) are associated with illicit drug use. As in many other countries, MMT in Canada is the standard of care for heroin treatment. But MMT has its limitations: it is available to a limited number of opiate-dependant users in Canada (only 15-20%), program coverage varies from province to province and where methadone is available it is not desirable or effective for some dependent users. Heroin prescription for treatment-resistant heroin users was recommended

as early as 1972 in the Commission of Inquiry into the Non-Medical Use of Drugs led by Mr. Justice Gerald LeDain. The NAOMI (North American Opiate Medication Initiative), a randomized controlled study of HAT is the first of its kind in North America and is taking place in Vancouver and Montreal. The NAOMI project is discussed in greater detail later on in this document.

In conclusion, there is a significant body of evidence that HAT helps stabilize those heroin-dependent users who are unresponsive to other treatment by improving physical and mental health, increases social integration, reduces high risk behaviour, prevents overdose, reduces dependence on street heroin and reduces involvement in illegal activities. For some patients HAT has shown to be the first step towards MMT or even abstinence. HAT has also been clearly shown to be a cost effective intervention for the treatment of resistant heroin users.

Stimulant Replacement Therapy

Stimulant substitution therapies, similar to opiate substitution, consist of replacing the illegal and harmful stimulant drug --such as cocaine, crack cocaine or methamphetamine-- with a legal substance and often a safer route of administration. The goals of this treatment are to stabilise the user with doses that prevent withdrawal and to reduce the attendant harms of illegal drugs including criminal activity, reliance on the black market, blood-borne diseases and overdose deaths. Changing the mode of administration from intravenous to oral use can be particularly effective for cocaine dependency, where injection use is frequent.

In Vancouver, with its high prevalence of HIV among injection drug users (from 17% to 31% in different cohorts) injection cocaine use is the strongest predictor of contracting HIV, as indicated in a 2005 study. In addition, users often use cocaine and heroin concurrently, as is certainly the case in the DTES, along with crack cocaine use which is high in the DTES and among survival sex workers.

Unlike opiate treatment, which offers well-established substitution programs (such as MMT in several countries and HAT in a few), no such treatment is available yet for stimulant use because the development of appropriate medicines has been problematic. The search is ongoing and the list of medications tested for treating stimulant dependence is long. For example, the National Institute of Drug Abuse in the US has tested 42 different medications just for the treatment of cocaine (see appendix 1).

Several other studies have been executed or are currently being conducted in other countries for both cocaine and amphetamine dependence, with pharmacological and psychosocial treatment. Some promising results from various trials have surfaced, warranting further research in the area of stimulant substitution.

The case of Britain, once again, is unique. For several decades, along with heroin general practitioners have been allowed to prescribe amphetamines to stimulant-dependent users. A 1995 survey of community pharmacy services for drug users in England estimated 900-1,000 patients were receiving treatment, usually prescriptions for dexamphetamine tablets and oral liquid. There were no controlled studies but the practice was considered clinically successful by amphetamine-prescribing physicians, of which there were 200.

Several substances currently being looked at in various clinical trials include dextroamphetamine, methylphenidate, modafinil and adderall, among others. Studies in

stimulant substitution have had the disadvantages of being short in duration and having small cohorts of subjects. Results have been promising and have included a reduction in opiate use as well as reduction of stimulant use. Some studies have shown a decrease in criminal activity, a reduction in injecting behaviour; in one study 13% of participants became abstinent. Retention in treatment, a key indicator of success for treatment programs, was significant in some of the studies.

Other studies have been less conclusive and have faced challenges such as high attrition rates and inconclusive results.

In conclusion, as compared with opiate substitution, research for stimulant substitution is still in its infancy and further research efforts are warranted to increase knowledge in this area. Given the preponderance of stimulant use in Vancouver, local research could significantly add to the interventions available for the treatment of stimulant addiction.

See appendix 1 for fuller descriptions of several stimulant substitution trials.

North American Opiate Medication Initiative (NAOMI)

Funded by the Canadian Institutes of Health Research (CIHR), this randomized controlled clinical trial is testing whether medically prescribed heroin assisted therapy (HAT) benefits chronic treatment-resistant opiate addictions started in February 2005 in Vancouver and June 2005 in Montreal. Those accepted into the program had to be 25 or older, addicted to heroin for at least five years, with daily injection use for at least one year. They must also have attempted at least two episodes of MMT (or MMT and another form of treatment) for 30 or more consecutive days. The NAOMI study is examining whether HAT can stabilize dependent users and improve their heath and social integration.

Participants were randomly assigned to oral methadone treatment or the injection group. In the second group, most received injectable pharmaceutical heroin, while the remaining participants received injectable hydromorphone, or dilaudid, which is an analgesic pharmacologically similar to heroin. Those receiving injections are able to receive MMT as well. All participants have access to social workers, drug and alcohol counsellors, nurses and primary care physicians. The study hypothesizes that there would be better retention rates, less illicit drug use and less criminal behaviour with HAT than MMT for treatment-resistant users. The study will also provide an analysis of the cost-effectiveness of this treatment.

NAOMI is now closed for enrolments. Although recruitment was slow initially, the trial met its target with a final total of 251 patients registered (192 in Vancouver, 59 in Montreal). Approximately half of the participants have completed the treatment phase of the study. The treatment phase of the study continues for 12 months, followed by a three-month period during which participants still being treated with injection drugs can transition to conventional therapies, such as MMT or abstinence-focused therapies.

The last of the participants enrolled this past spring will complete the treatment phase in June 2008. Although not yet official, some outcomes are already obvious, such as treatment retention at the end of a 12-month period: approximately 50% and 85% in the oral and injection arms respectively.

A unique feature of NAOMI is the small sample (10%) of patients receiving dilaudid. As this was a double blind randomized controlled trial neither patient nor physician were aware who was actually receiving dilaudid. Preliminary data shows that from those receiving it, none suspected it was not heroin.

The NAOMI project will be reporting results in late 2008.

Inner Change Society and Chronic Addiction Substitution Treatment (CAST)

The Inner Change Society was set up in early 2007 for the purpose of initiating a treatment program for the most difficult to reach drug addicts; this program has been named **Chronic Addiction Substitution Treatment** (CAST). The members of this charitable organization are convinced that it is necessary to support the city by private fundraising and other initiatives to address one of the biggest challenges in Vancouver, the health crisis in the Downtown Eastside (DTES).

The Inner Change Society is looking for close cooperation with many experts in the field, including family and user organizations. The scientific advisory board is chaired by Dr.David Marsh, the physician leader for Vancouver Coastal Health in Addiction and Aboriginal Health.

Currently, Inner Change has supported work towards the development of five clinical research trials that will be put forward to Health Canada for approvals. The society is seeking funding sources for the research trials from a range of government, foundation and private sources.

The Clinical trials plan to focus on the most problematic drug-using populations in Vancouver and will add to the complement of interventions currently underway in the city. The five trials being developed include:

- Integration of HIV treatment and addiction treatment. This trial will focus on drug users who are living with HIV and are stimulant users. Participants will have access to state of the art HIV treatment, psychosocial interventions and participants will be offered an oral stimulant substitution. The study will look at how effective addiction treatment combined with HIV treatment can benefit patients and the community. The sample size for this clinical trial will be 100 individuals.
- Optimized Opioid Substitution clinical trial. This trial will consider substituting several substances that have been used in other jurisdictions for heroin users; it particularly targets those who are not doing well with existing treatments. They include Polamidon, a form of methadone with fewer side effects, slow release oral morphine, Suboxone, a combination of buprenorphine and naloxone, and methadone. Psychosocial interventions will be offered to all participants. The sample size for this clinical trial will be 400 individuals – 100 to be given one of the four trial substances.
- Heroin Assisted Treatment vs Hydromorphone, intravenous vs oral administration. This trial will take place in two phases. Phase 1 will involve

randomizing participants into two treatment arms, those in the one arm receiving diacetylmorphine (heroin) as part of the treatment regime and those in the second arm receiving hydromorphone (available in Canada e.g. as Dilaudid). The second phase of the clinical trial will randomize %50 of each arm to oral routes of administration to test whether this methode of administration can be as effective as injection of these substances. Psychosocial interventions will be offered all participants.

- The treatment of stimulant dependence. This trial will focus on heavy stimulant users and compare three approaches to treatment: psychosocial, pharmacological and work focused rehabilitation. All participants will be offered psychosocial treatment with some participants being randomized to receive either an oral slow release amphetamine substitution or a placebo. Participant will also be randomized into an employment related rehabilitation program. The sample size for this clinical trial will be about 400.
- Treatment of crack users with contingency management and amphetamine substitution. Contingency management refers to a treatment plan that gives rewards for desired changes in behaviour based on the notion that if a good behaviour is rewarded it is more likely to be repeated. This trial will consider a larger sample of 1000 individual crack and cocaine users. Case management and psychosocial treatment will be offered all participants in addition to contingency management, psychoeducational group work and an oral stimulant substitution treatment. The primary outcome that this trial will look at is level of stimulant use among the participants.

It should be noted that at this point these clinical trial proposals are under construction and are in draft form. One Letter of Intent has been submitted to CIHR and another Letter of Intent for a second trial will be submitted in October.
The Inner Change Society has contracted with an executive director to coordinate the research and fundraising efforts for the clinical trials.

In two previous Council reports staff have recommended expanding substitution treatment options for drug users in Vancouver. Given the prevalence of stimulant use in the community exploring new and innovative approaches to these populations fits well within the ongoing efforts to build a more comprehensive system of addiction treatment for Vancouver. The Inner Change Society has some significant but not insurmountable challenges to address before implementation can occur. Securing the regulatory approvals will take considerable time and effort and securing funding for these trials will be a critical piece of work. The work of the Inner Change Society in developing the CAST project fits into the Four Pillars Drug Strategy in the same way that other projects such as the supervised injection site or efforts to expand youth treatment programs do. In this regard City staff review the evidence base for these kinds of interventions and if warranted provide information, advice, analysis and generally support the development of new and innovative projects in order to increase the offerings for those with addictions in Vancouver.

FINANCIAL IMPLICATIONS

There are no financial implications.

CONCLUSION

Some forms of drug substitution and maintenance have a long track record and the evidence from other countries suggests that these kinds of programs can make a significant contribution to the attempts to tackle Vancouver's drug problems. While stimulant research is at an earlier stage than work to date on opiate replacement programs, initial results indicate some promise, leading to calls for more research in this area. In addition, psychosocial treatment has shown good evidence in the treatment of cocaine users in the United States. Combining pharmacological treatment with psychosocial treatment may increase treatment outcomes. Methadone maintenance treatment should be expanded in Vancouver in order to engage more opiate users in treatment. Based on experiences in other countries, it would be well worth further exploring heroin replacement treatment, in order to reach out to users who are not successful with methadone treatment. Of course these treatments will be most effective as part of a comprehensive approach to Vancouver's drug problems, where treatment is offered as part of a strategy that also includes supported housing and programs to reintegrate individuals into the community.

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DEPARTMENTAL APPROVAL AND REPORT CONCURRENCES

General Mgr./Dept. Head:	**Report Date:** September 21, 2007
	Author: Zarina Mulla/Donald MacPherson
Date:	**Phone No.:** 604.871.6040
This report has been prepared in consultation with the departments listed to the right, and they concur with its contents.	**Concurring Departments:**

Appendix 1

Drug Substitution and Maintenance

An Overview of Opiate and Stimulant Substitution and Maintenance Research

Introduction

Addiction to psychoactive drugs is a complex condition involving a malfunction of neurotransmission or a disruption of brain chemistry under the effects of these substances. It is typically characterized by craving, withdrawal and compulsive use, despite severe negative consequences. It is generally accepted today that addiction is a multifaceted, bio-psycho-socio-spiritual phenomenon, both in terms of causes and consequences, and that a range of treatment responses are required to best address the diverse manifestations of this condition.

Over the years, our understanding of addiction has progressively matured. Viewing it as a medical, behavioural, social and environmental problem instead of a moral or criminal one has allowed for the development of better treatment modalities during the last few decades. The search for long-term treatment methods has led to the concept of opiate maintenance. Drug maintenance and substitution treatment replaces one addictive drug with a safer, legal prescription drug within a course of treatment that usually includes psychosocial and other non-pharmacological interventions. The objectives of drug substitution and maintenance treatment include: stabilizing patients until they are ready to reduce or cease their drug use; reducing their dependence on the black-market with all its associated harms; reducing criminal activity; prevention of blood-borne disease and overdose deaths; and improving patients' personal, social and family relations (Hunt, 2003). The value of opiate maintenance was well understood in UK in the early 1900's and was instituted as a treatment method as early as 1926. (A longer discussion on the British approach is dealt with later on in this document). In the USA, from 1914 to 1924, morphine maintenance programs were established in New York City and other jurisdictions; more than 7,000 patients were prescribed opiates in an attempt to stabilize them. This strategy was soon outlawed by the US supreme courts (Drucker, 2000).

In recent years, as the use of stimulants such as cocaine, crack cocaine and methamphetamine have become more prevalent, addiction researchers have turned their attention to the prescription of a variety of pharmaceutical stimulant products to see if similar results to those seen with opiate maintenance programs can be achieved with stimulant substitution and maintenance treatment. This report will summarize the growing body of evidence that indicates promising results in these areas of substitution and maintenance treatment.

Opiate Substitution

Methadone

During the 60's in the US, the problems of heroin addiction were becoming increasingly visible outside the usual circles of jazz and bohemia to which it had been confined up to that point. A young psychiatrist from New York's Harlem, Dr. Marie Nyswander started prescribing various opiate compounds, in an attempt to help her patients stabilize themselves. She combined her efforts with Dr. Vincent Dole, a researcher from the Rockefeller University and together they began using a form of a synthetic opiate called methadone for opiate maintenance (Drucker, 2000).

Methadone is a legal long-acting synthetic opiate or opiate used in the treatment of heroin dependence. It is a synthetic opioid agonist[2] with the same molecular structure as heroin and has two advantages over it as a long-term maintenance substance: it can be given orally and it has a longer half-life – 24 to 36 hours as compared to two to three for heroin. This meant that a single daily dose provided under supervision could help combat withdrawal, eliminate the need for black-market heroin and, in many cases, drug-related crime thus eventually stabilizing the patient to function normally and be part of society. In spite of being a potent opiate, for some patients with higher tolerance it failed to produce a high, which was another important strike in its favour.

Over the last four decades methadone has been clinically tested through several studies and rigorous randomized control trials which have established its effectiveness in establishing positive health outcomes for chronic opiate-dependent patients (Drucker, 2000). It has successfully demonstrated its effectiveness in withdrawal management and in the reduction of criminal activity, unemployment, mortality rates and in opiate use leading, in some cases, to eventual abstinence (Kerr, 2006).

In Vancouver, 76 licensed pharmacies provide methadone maintenance treatment to a total of 2,729 patients. Thirteen of the 76 pharmacies are located in the DTES, with a clientele of 1,195 patients (CoV Statistics).

Buprenorphine

This treatment is available in several countries in Europe: France, Denmark, Austria, Finland, Luxemburg and the U.K. It has been licensed since 2002 in the U.S. and recently in Canada. Although not as extensively studied as methadone, it has been investigated for its efficacy as an opioid replacement therapy. Due to its mixed agonist/antagonist properties, the risk of overdose appears to be eliminated. Moreover, since it has a longer half life than methadone, it can be dispensed every other day. A review undertaken by Mattick et al, comparing buprenorphine to methadone and placebo indicates that buprenorphine is more effective over placebo

[2] An agonist is a compound that enhances the activity of a neurotransmitter. It binds to the receptor site to induce a full chemical response. A long-acting agonist like methadone provokes a response thus alleviating symptoms of withdrawal. An antagonist is a compound that blocks the neurotransmitter. It occupies the same receptor as the addictive drug inhibiting a response thus denying access to the drug e.g. Naltrexone blocks heroin and has no mood-altering properties. It is commonly used to reduce the risk of relapse after detox or drug free programs.

for heroin maintenance but, when compared to higher doses of methadone, it has lower retention rates and less suppression of heroin use. The review concludes that buprenorphine should be used when higher doses of methadone cannot be prescribed (Hunt, 2003).

According to a World Health Organization (WHO) report, 10% of the estimated 12.6 million IDUs in the world are HIV-positive and treatment of heroin users through substitute maintenance is one of the critical interventions to combat the HIV epidemic globally. Methadone and buprenorphine have recently been included in the WHO list of essential medicines (WHO, 2006)

Despite its benefits, however, and its well-researched reputation making it the most common drug for heroin substitution, methadone is not effective or desirable for some treatment patients.

Heroin Prescription

The prescription of heroin as part of a treatment regime for heroin-dependent users has been available in the UK since 1926. The Rolleston Committee, set up by the Home Office to advise the British Government on whether drug maintenance treatment was appropriate, determined that addiction was indeed a medical issue and that maintenance treatment had an important role to play in the treatment of drug addiction . More recently, four countries (Switzerland, Netherlands Germany and Spain) have successfully conducted studies on its efficacy, two more (UK and Canada) are in the process of conducting trials and awaiting results and one (Belgium) is scheduled to start soon. Summarized below, according to country, are the backgrounds, findings and conclusions of some of these studies.

SWITZERLAND

Background

In the early 1990s, escalating problems from heroin use including severe public nuisance, negative public attitudes and increasing health costs from a soaring prevalence of HIV forced the Swiss government to re-examine its drug policy, thus laying the foundation for the fourfold approach of prevention, law enforcement, harm reduction and therapy. As compared to other countries, the Swiss drug policy was more effective as it was able to reach and treat a relatively high proportion of drug-dependent users. However, a small number of heroin users failed to respond successfully to the available abstinence-oriented or methadone maintenance treatments. Consequently, the Federal Council requested a scientific study and a Swiss research project was established in 1994 to ascertain the effectiveness of other opiates to treat heroin addiction in the most refractory users. Over time, the focus of this project was readjusted to become a cohort study on heroin-assisted treatment (HAT). HAT was first tested in the National Cohort Study between 1994 and 1996.

Results as recorded in 1999 included the following:

Crime

- Income from illegal activity (determined by police records and individual

testimony) decreased from 70% to 10%
- Offenders and offences decreased by about 60%
- Shoplifting decreased from 35% to 16.1%
- Breaking and entering decreased from 6.9% to 0%

Social Integration
- Homelessness went down from 12% to 1 %
- Unstable housing rate fell from 43% to 21%
- Employment rates grew from 14% to 32%
- Debts during the treatment period were substantially reduced
- Contact of patients with the drug scene fell from 29% to 2%

Cost Effectiveness
- Savings in criminal investigation, prison days and health improvements
- Net economic benefit of $40 (45 Fr) per patient-day (approximately $15,000 Cdn per person per year)

Other
- From the 200 persons leaving the program per year, approximately 50 patients switched to abstinent-based treatments while almost 90 switched to methadone.
- General health improved; marked decrease in injection-related skin diseases
- Illicit heroin and cocaine use decreased rapidly (Uchtenhagen, 1999)

Conclusions

> In a referendum in 1997, a majority of 71% of voters were in favour of heroin prescription. On March 8, 1999 the Federal Council authorized HAT throughout Switzerland, thus firmly establishing it as part of its treatment pillar. Patient numbers have steadily increased over the years. From fewer than 800 in 1998, in 2005 there were a total of 1,428 clients undergoing HAT in 21 outpatient centres and two prisons (FOPH, 2006). HAT enrolment makes up about 5% of all Swiss drug users in treatment (Wodak, 2005).

Another study conducted by Rehm et al., assessing 1,969 opioid-dependent drug users who began HAT between 1994 and 2000 found: more than 70% of patients remained in the program for more than a year; participants showed positive health and social outcomes; and there was a direct correlation between the clients' length of treatment and chances of starting abstinence-oriented therapy. The study found HAT was cost-beneficial to Swiss society with a marked improvement in medical and social variables including criminality (Rehm, 2001).

A study published in the *Lancet* in 2006 puts to rest the criticism leveled at the Swiss that their "liberal" drug policy would attract new users and encourage drug use. The trends of heroin use incidence in Zurich show that in 1975 there were 80 new users, which increased to 850 in 1990 and declined to 150 in 2002. The authors concluded that the medicalization of heroin through HAT and MMT prescription made it less

attractive to young people, which in turn contributes to the decline in the population of problematic heroin users as compared with other countries (Nordt, 2006).

NETHERLANDS

Background

It is estimated that there are 25,000 heroin-dependent users in Netherlands (total pop. 16 million). Despite a comprehensive network of treatment and harm reduction services, approximately one-fourth of the users on methadone maintenance tend to use illegal heroin and have attendant problems of mental and physical health, social exclusion and crime. In 1996, the Minister of Health, Welfare and Sports authorized the Central Committee on the Treatment of Heroin Addicts (CCBH) with the task of reporting to the Minister about the effects of medically prescribed heroin on heroin users displaying poor response rates to other treatments.

Description of Study

Two open-label, randomized control trials were conducted with a total of 549 patients between 1998 and 2001. The interventions consisted of injectable or inhalable heroin plus methadone, compared with methadone alone. Throughout the treatment, psychosocial support was made available. The objective was to determine whether supervised medical prescription of heroin can successfully treat users resistant to methadone maintenance treatment. It was conducted in six cities.

Results

- Good adherence rate to treatment
- Heroin, both injectable and inhalable, plus methadone was found to be significantly more effective than methadone alone
- For those responding to the co-prescribed heroin, a sudden discontinuation led to a rapid deterioration. Eighty-five percent of patients transferred at the end of HAT to MMT deteriorated (van den Brink, 2003).

Conclusions

Co-prescription of heroin is feasible and more effective than methadone alone in reducing the many physical, mental, and social problems of treatment-resistant, heroin-dependent users

The Dutch heroin trials mentioned above established that supervised medical prescription of heroin is safe and that it improves physical, mental and social functioning, including crime reduction, in chronic, treatment-resistant heroin users. But is it cost effective? Heroin prescription on a daily basis has a number of expensive health and security measures associated with it. Do the ensuing benefits result in actual cost savings? A study was conducted with the objective of determining the cost utility of medically prescribed heroin, compared with MMT for chronic treatment-resistant heroin users. An economic analysis was carried out on 430 of the 549 patients from the Dutch Heroin trials.

Results:

- Supervised medical co-prescription of methadone and heroin is less costly than methadone maintenance treatment

- Co-prescription of heroin was associated with 0.058 more Quality Adjusted Life Years[3] per patient per year and a mean saving of $19,000 Cdn per patient per year
- The higher program costs were compensated by lower costs to the criminal justice system and damage to victims of crime

Conclusions:

- In the case of chronic, treatment-resistant, heroin-dependent users, co-prescription of heroin is cost effective, compared with treatment with methadone alone (Dijkgraaf, 2005).

GERMANY

In Germany, after many years of discussion, the Bundestag authorized a pilot project for heroin-assisted treatment. Thus, in 2002, the Federal Ministry of Health, three federal states and seven cities partnered to conduct a three-year trial. By the end of 2003, a total of 1,032 participants were recruited and by the end of 2004 the first phase of the project was completed. The 434 participants who completed the first phase took part in the second 12-month phase, which terminated in 2005. Results were favourable and are described in detail below. All participants who completed the heroin-assisted treatment took part in a follow-up phase which continued until December 31, 2006.

Description of Study

The design of this randomized multi-centre study consisted of two sample strata:

1. Methadone treatment failure (MTF) or MMT-resistant heroin users
2. Not reached or NR; those who were out of reach of the treatment system

Each of these two major groups was randomized to four groups: two experimental groups treated with heroin and one of a range of psychosocial treatments (psychoeducation/drug counseling vs. case management/motivational interviewing) and the same for the control group treated with methadone and one of a range of the same psychosocial treatments. Thus all of these eight groups received study treatment for a period of 12 months within the first phase.

The second phase with 434 participants consisted of 344 from the experimental group who had completed the heroin-assisted treatment in the first phase, plus 90 from the control group who had the opportunity to switch to the heroin-treatment spots left vacant from the first phase. The design of this phase consisted of four groups of equal size and they were the following:

1. MTF, heroin treatment and psychoeducation
2. MTF, heroin treatment and case management
3. NR, heroin treatment and psychoeducation
4. NR, heroin treatment and case management

Objectives

[3] Quality-adjusted life years, or QALYs, assess the quality and quantity of life lived as a means of computing the benefit of a medical intervention.

The first study's objective was to determine if the prescription of diacetylmorphine (DAM) -which is pharmaceutical-grade heroin - is more effective than methadone treatment in stabilizing refractory clients. The second study's objective was to ascertain whether medically prescribed DAM over a longer term can enhance the improvements made in the first study, focusing on outcomes such as reduction of illicit drug use, mental and social well being, overcoming addiction and integration into addiction services.

Results

The heroin group showed better results overall than the control methadone group. The superiority of heroin over methadone treatment was even more apparent in the 90 who switched to heroin treatment in the second phase. The results at the end of the 24-month period showed that the switchers had managed to catch up and display the same outcomes as the two-year heroin patients. Results include:

- A high retention rate – 55% of the 515 randomized to the heroin arm were still in treatment after two years. The retention rate was higher in the second year. Among MTF patients it was higher than in NR patients. Nearly 50% who discontinued heroin treatment switched to methadone or buprenorphine. Ten percent went into abstinence treatment.
- Improvements in physical and mental health, with significant improvements in physical health in the second year
- Similarly, a decline in cocaine use in the first year and even more in year two
- A sharp decline in street heroin use was maintained in the second year
- Connected to the decrease in illicit drug use and the distancing from the drug scene, there was a marked decline in criminal behaviour in the first phase and a slight improvement in the second
- An impressive decline in high-risk behaviour, like needle sharing, with a complete drop in both groups (heroin and switchers) in year two
- An 11% increase in employment in the first year and 27% in the second year

Conclusions

In the case of treatment-resistant heroin users, heroin-assisted treatment was found to be superior in a statistically significant way over methadone treatment (Naber, 2006).

U.K.

Background

Prescribing opiates has been part of the British approach for treating opiate addiction since 1926, when a report by the Departmental Committee on Morphine and Heroin Addiction established doctors' right to prescribe it. Over the following three decades that this practice continued, there was no evidence to suggest that heroin prescription had led to an increase in the number of heroin-dependent users. The situation, however, changed in the 1960s. Heroin prevalence was on the increase globally; in the UK, heroin prescribed by some GPs was leaking into the burgeoning black market. Concerns regarding this led to the Brain Report in 1965 which recommended some significant changes to the practice of heroin prescription.

Subsequently, heroin could be prescribed only by those doctors holding a special license and doctors were obligated to report to the Home Office on the number of dependent users treated. It was also recommended that special outpatient clinics for the purpose of prescribing heroin should be set up, the rationale being that they would decrease drug crimes by providing free heroin to the user, reduce harm to the user by maintaining heroin purity and deter black marketing by bringing heroin under tighter control. The clinics provided prescription heroin and in some cases injectable methadone. Gradually, this gave way to injectable and ingestible methadone, the main rationale for this being that methadone reduces the need to inject frequently. In the mid 70's, there was a dramatic rise in the prescription of injectable methadone, which led to a drop in heroin being prescribed and, eventually, oral methadone surpassed both as the preferred treatment of the day (Bammer, 1997; Gilvarry, 2005).

Although, the UK has a long history of heroin prescription, there is a lack of systematic research on the subject (Carnwath, 2005). Also, the practice is rare, few doctors engage in it, and the figures reported are incomplete since not all doctors notify as required. According to a survey in 2000, of the 70 doctors licensed to prescribe heroin, 46 were actually prescribing to 448 patients. Methadone, however, was the main drug prescribed by most (Stimson, 2003).

Recent numbers of heroin-dependent users in the UK are estimated at 300,000 (Tendler, 2006) and an estimated 128,000 on methadone treatment **(**EMCDDA). However, not all clients respond adequately to the methadone treatment.

Heroin Trials

In an effort to reduce crime, and encouraged by evidence from Switzerland and the Netherlands, the UK's National Health Service has embarked upon three trials with 150 chronic heroin-dependent users. Results will be announced in late 2007. Typically, a heroin-dependent user in the UK needs $34,000 Cdn/year to fund their heroin addiction and incurs costs of $100,000 Cdn/year in crime. It is estimated that up to 60% of crime is drug related; this would decline significantly as a result of heroin prescription. Currently, heroin maintenance is estimated to cost $27,000 Cdn per person. Economic savings from crime reduction, it is expected, would far outweigh the cost of heroin maintenance (Tendler, 2006).

SPAIN

Background

Methadone treatment is widely available in Spain. However, as in the case of other countries in the world, many are not able to respond to the treatment or give up use of illegal heroin. These users are typically severely marginalized, suffer from acute physical and mental problems and have tried and failed methadone treatment for several years. A search for treatment alternatives for this profile led to the examples of other countries where the feasibility, safety and efficacy of intravenous

diacetylmorphine (DAM) has been clinically proven. However, further research was warranted to generalise these results for the local population.

Description of Study
The objective of this open randomized control trial in Granada, Spain was to assess the efficacy of DAM over oral methadone with medical and psychosocial support. DAM plus methadone was prescribed to an experimental group of half the randomly assigned 62 clients, while a control group with the other half received oral methadone only. Outcome measures included physical, social and psychological health, quality of life, addiction-related problems and risk behaviour for HIV.

Results:
While both groups improved, the experimental group fared better in terms of physical health, risk behaviour for HIV and reduced drug-related problems and street heroin use

Conclusions:
Further research concluded that DAM could be safely delivered in the local context and that DAM plus methadone was more effective than methadone alone for the treatment of recalcitrant, socially marginalised, severely addicted and physically and mentally affected opioid patients
(March, 2006).

BELGIUM
This fall, Belgium is scheduled to begin a three year experiment in Liege supported by the Ministries of Public Health and Justice. A total of 200 heroin users will be randomized equally either with pharmaceutical heroin or methadone to test the efficacy of heroin-assisted treatment over methadone. All participants will also receive medical and psycho-social treatment (CEEHRN).

CANADA
About 60,000-90,000 Canadians are addicted to heroin; many live in Vancouver, Montreal and Toronto. They face the risks of lethal overdoses, exposure to HIV and Hepatitis C and tend to be involved in drug-related violence and crime. A recent Canadian study estimated that every person addicted to heroin generates $45,000 in social costs per year.

As in many other countries, in Canada MMT is the standard of care for heroin treatment. But MMT has its limitations. It is available to a limited number of opiate-dependant users (in Canada, only 15-20%) and where it available, it is not accepted by all. A Toronto survey showed that if MMT was made available, only 48% of users would accept it, 33% would reject it and 19% were undecided. Approximately 15%-20% of the

estimated opiate addict population is in MMT, with higher numbers in metropolitan centres.

For some, however, MMT is ineffective. Evidence from Swiss, Dutch and German studies examining the effectiveness of heroin prescription in the treatment of heroin-dependent users who have not benefited from other treatment modalities has been encouraging, including drops in heroin-related crimes. Heroin prescription for treatment-resistant heroin users has been recommended since 1972 in a Commission of Inquiry led by Mr. Justice Gerald LeDain.

North American Opiate Medication Initiative (NAOMI)
Funded by the Canadian Institutes of Health Research (CIHR), this randomized controlled clinical trial is testing whether medically prescribed heroin therapy (HAT) benefits chronic treatment-resistant opiate addictions started in February 2005 in Vancouver and June 2005 in Montreal. Those accepted into the program had to be 25 or older, addicted to heroin for at least five years, with daily injection use for at least one year. They must also have attempted at least two episodes of MMT (or MMT and another form of treatment) for 30 or more consecutive days. The NAOMI study is examining whether HAT can stabilize dependent users and improve their heath and social integration.

Participants were randomly assigned to oral methadone treatment or the injection group. In the second group, most received injectable pharmaceutical heroin, while the remaining participants received injectable hydromorphone, or dilaudid, which is an analgesic pharmacologically similar to heroin. Those receiving injections are able to receive MMT as well. All participants have access to social workers, drug and alcohol counsellors, nurses and primary care physicians. The study hypothesizes that there would be better retention rates, less illicit drug use and less criminal behaviour with HAT than MMT for treatment-resistant users. The study will also provide an analysis of the cost-effectiveness of this treatment.

NAOMI is now closed for enrolment. Although recruitment was slow initially, the trial met its target with a total of 251 patients registered (192 in Vancouver, 59 in Montreal). Approximately half of the participants have completed the treatment phase of the study. The treatment phase of the study continues for 12 months, followed by a three-month period during which participants still being treated with injection drugs can transition to conventional therapies, such as MMT or abstinence-focused therapies.

The last of the participants enrolled this past spring will complete the treatment phase in June 2008. Although not yet official, some outcomes are already obvious, such as treatment retention at the end of a 12-month period: approximately 50% and 85% in the oral and injection arms respectively.

A unique feature of NAOMI is the small sample (10%) of patients receiving dilaudid. As this was a double blind randomized controlled trial neither patient nor physician were

aware who was actually receiving dilaudid. Preliminary data shows that from those receiving it, none suspected it was not heroin.

Stimulant Substitution Research

Stimulant substitution therapies, similar to opiate substitution, consist of replacing an illegal and harmful stimulant drug like cocaine or amphetamine with a legal alternative and a safer mode of drug use. The goals of this treatment are to stabilise the user with doses that prevent withdrawal and to reduce the attendant harms of illegal drugs, including criminal activity, reliance on the black market, blood-borne diseases and overdose deaths. Changing the mode of administration from intravenous to oral use can be particularly effective for cocaine dependency, where injection use is frequent. In Vancouver, with its high prevalence of HIV among IDUs (from 17% to 31% in different cohorts) injection cocaine use is the strongest predictor of contracting HIV, as indicated in a 2003 study (CCENDU, 2005). In addition, there are often concurrent users of cocaine and heroin, as is certainly the case in the DTES, along with crack cocaine use which is high in the DTES and among survival sex workers.

The British approach mentioned earlier in this document allowed for the prescription of amphetamines to stimulant dependent users and has been practiced for a few decades. A 1976 document from Mitcheson et al reports on the treatment of amphetamine dependence by amphetamine prescription. The 23 participants in the study had used amphetamine for less than one year and were treated with injectable methylamphetamine. Retention was low: only three stayed beyond three months, but two of these reported abstinence from all drugs. This failure influenced the course of stimulant treatment over the next 20 years, until HIV emerged as a serious threat (Grabowski, 2004). A 1995 survey of community pharmacy services for drug users in England estimated 900-1000 patients receiving treatment, most of which were prescriptions for dexamphetamine tablets and oral liquid (Strang, 1997). There were no controlled studies but the practice was considered clinically successful by the physicians surveyed in 1998 by Fleming. He noted that there were some 200 English doctors prescribing amphetamines (Fleming, 1998).

Since then, many medications have been tested for stimulant substitution. Table 1 below lists medications tested in the U.S.

Table 1

List (modified) of medications tested for treatment of cocaine dependence by the U.S. NIH, National Institute on
Drug Abuse, Division of Research and Development; courtesy of Ivan Montoya, MD

Medications tested for cocaine/stimulant abuse and dependence (N=42)

Amantadine	Dextroamphetamine	l-dopa/carbidopa	Naltrexone depot
Aripiprazole	Dextropmetrophan	Lofexidine	Progesterone
Atomoxetine	Disulfiram	LY544344	Propanolol
Baclofen	Divalproex	Mecamylamine	Selegiline

Buprenophine	Dronabinol	Memantine	Sertraline
Bup/Naloxone	Fluoxetine	Methamphetamine	Tiagabine
Buproprion	Gabapentin	Methylphenidate	Topiramate
Clonidine	GBR12909	Methadone	Venlafaxine
Cocaine-Vaccine	GCP44352	Modafinil	Yohimbine
Desipramine	Hydromorphone	N-acetyl-aspartate	
LAAM	Naltrexone		

(Grabowski, 2004.)

To date, there is no approved medication for the substitution of stimulant drugs. There are, however, several medications that have been studied or for which trials are underway. A review of recent or ongoing research on some recommended medications is captured below.

Dextroamphetamine

Cocaine Dependence

Recently, different pharmacotherapies for stimulant addiction have been studied under controlled conditions. There is evidence of some promising results for cocaine dependency substitution. One example of this is a double-blind randomized clinical trial carried out by the Substance Abuse Medications Development Research Centre, University of Texas-Houston. Cocaine dependent users (n=128) randomly received a placebo or 15 to 30 mg of dextroamphetamine sulphate sustained release capsules at the start of the 12-week trial. After five weeks they received 30 to 60 mg for active groups. The subjects attended the clinic twice a week and received an hour of psychosocial therapy. Results were limited by high attrition rates and showed the following:

- Retention was optimum in the 15 to 30 mg group
- Illicit drug use as tested through urine samples was lowest in the 30 to 60 mg group (Grabowski, 2001).

A similar double-blind randomized clinical trial with identical dosing regimen for dextroamphetamine and in combination with methadone was carried out for concurrent cocaine and heroin users over 26 weeks. The results were compared to a parallel study of risperidone for cocaine dependence. All 240 patients received methadone and behavioural therapy but were equally divided into two studies, one randomized with dextroamphetamine and placebo and the other with risperidone and placebo. Results indicated that opioid use was reduced in all groups, with most reduction in the 30-60mg dextroamphetamine group. Cocaine use was most reduced in the 30-60 dextroamphetamine group, less in the 15-30 group and in placebo. There was no reduction at all in the risperidone group or placebo. The study provides support for dextroamphetamine (Grabowski, 2004).

Another double-blind, randomized, placebo-controlled trial was conducted in Australia with the aim of establishing feasibility and obtaining preliminary data. Thirty cocaine IDUs were assigned randomly to receive 60 mg of dexamphetamine daily for 14 weeks. Results showed that retention was equal in both groups; however outcomes were more noticeable in the treatment group than in the placebo-control

group. For example, the proportion of cocaine-positive urine samples declined in the treatment group from 94% to 56% but there were no improvements in the control group. The treatment group also showed a reduction in self-reported cocaine use, criminal activity, craving and dependence (Shearer, 2003).

Amphetamine Dependence
Several small treatment programs have been reported, mostly in England but also in Australia. Most have been uncontrolled, are reports or evaluations and have been implemented without specific research findings. A 1994 report by Fleming and Roberts describes a substitution program in Portsmouth, England treating 26 amphetamine injectors with oral dexamphetamine and group therapy. Finding showed:

- average retention was 15 months
- over 50% stopped injecting
- the rest reduced frequency of injecting
- 13% became abstinent
- criminal activity diminished

As psychosis is a potential adverse effect of dexamphetamine prescription among dually diagnosed patients, it has been argued such patients should be excluded from this treatment (Grabowski, 2004).

The first pilot, randomised controlled trials were conducted in 2001 in Sydney, Australia with the purpose of testing the feasibility of conducting a definitive randomized controlled trial of dexamphetamine substitution for amphetamine dependency. Out of the 41 patients, 21 were offered counselling and 20 were also prescribed 60 mg dexamphetamine. Findings showed that both groups showed reduced use of street amphetamine, reduced injecting behaviour and reduced dependence, with a greater --although not significant-- reduction in the dexamphetamine group (Shearer, 2001).

Lisdexamfetamine Dimesylate (NRP104)
At a December 2006 conference in Sydney Australia, Grabowski spoke of yet another promising oral drug (in addition to dextroamphetamine) under development for ADD called NRP104, which will be commercially available in a couple of years (*The Australian*, 2006). As evidenced by three studies comparing this drug to dextroamphetamine, the abuse potential for NRP104 was low as it tended to be less euphoric and had a later peak effect, which is unappealing to drug users seeking a quick effect (*Medical News Today* 2006).

Methylphenidate
Cocaine Dependence
Methylphenidate(MPH) is an amphetamine-like substance used in the treatment of ADD, narcolepsy and chronic fatigue syndrome; it is found under brand names such as Ritalin. Some studies have been carried out using it for the maintenance of cocaine-dependent users with ADD symptoms. The results have been complicated and inconclusive but, at the very least, it can be safe to say that this treatment has value

for cocaine-dependent users diagnosed with ADD. A recent double-blind clinical trial with 106 ADD diagnosed cocaine-dependent users compared the efficacy of MPH with placebo in treating ADD. The MPH group reported improvements in ADD symptoms and a decrease in cocaine use (Levin 2007).

Amphetamine Dependence
A recent double-blind randomized trial aimed to compare the effectiveness of methylphenidate, aripiprazole, and a placebo in the treatment of amphetamine dependence. A group of 53 intravenous amphetamine users was randomly assigned to the three groups for a period of 20 weeks. Finding indicated that MPH treatment was more effective in reducing intravenous amphetamine use as compared to the other two groups (Tiihonen 2007).

Topiramate and Adderall-XR
Cocaine Dependence
Topimarate was evaluated in a trial with 40 cocaine-dependent users. The experimental group were more likely to be cocaine-abstinent than the placebo controlled one. Several trials are currently underway on a larger scale, mostly by the National Institute of Health and the National Institute on Drug Abuse (NIDA) in the U.S. but also by the Hadassah Medical Organisation, Jerusalem.
Adderall, a combination of mixed amphetamine salts and dextroamphetamine is an alternative medication to Ritalin (methylphenidate), and is often prescribed when Ritalin is not effective. Adderall has a longer half life and hence can be administered half as frequently. A current study by NIDA is planning to test the safety and efficacy of Topiramate and Adderall-XR. The study is based on the premise that since both of these drugs have independently shown promise in treating cocaine dependence, they would be even more effective together. The study plans to recruit 120 cocaine-dependent persons in a 14-week randomized, double-blind, placebo-controlled trial. It plans to measure cocaine abstinence and cravings
Modafinil
Cocaine Dependence
Described as a wake-promoting agent, this drug has been generally prescribed for the treatment of narcolepsy and sometimes for ADD. Due to its properties of promoting wakefulness and alertness, it may also have utility for the treatment of stimulant withdrawal symptoms, such as hypersomnia, low mood and lack of concentration. Case reports have shown positive results for the treatment of withdrawal from cocaine and amphetamine dependence with no significant potential for abuse (Shearer, 2004). Currently, trials are underway to test its validity in the treatment of cocaine and amphetamine dependence.

In the U.S., NIDA has been recruiting patients in a double-blind, placebo-controlled trial to evaluate the efficacy of modafinil in treating cocaine dependent patients (n=210) since July 2004. The study will aim to measure the effectiveness of this treatment in improving cocaine abstinence during early recovery from cocaine dependence. It will also measure its effectiveness in reducing cravings and improving retention. Participants will be randomized to two groups, one receiving modafinil and

the other a placebo for a period of eight weeks, after which treatment will be abruptly discontinued, followed by an evaluation the following week and further evaluations three and five months after the initial randomisation. Those who discontinue the modafinil treatment will continue to be evaluated.

NIDA is also conducting trials on the effectiveness of modafinil and dextroamphetamine, alone and in combination for cocaine dependence.

Cocaine and Amphetamine Dependence
The University of New South Wales and the Australian Government Department of Health and Ageing is currently recruiting patients in two randomized placebo-controlled trials: one for cocaine (n=30) and the other for methamphetamine dependence (n=60). Primary outcome measures for both studies are compliance, retention, adverse effects and negative urine analysis to measure stimulant abstinence. Secondary outcome measures for both are self-reported drug use, health outcomes and psychosocial outcomes. Both studies aim to test the safety and effectiveness of modafinil over 10 weeks, together with a cognitive behavioural therapy program in the treatment of stimulant dependence. Patients will be randomized to two equal groups: the experimental group will receive a daily dose of 200 mg and cognitive behavioural therapy while the control group will receive a placebo and similar cognitive behavioural therapy

Inner Change Society and Chronic Addiction Substitution Treatment (CAST)
The Inner Change Society was set up in early 2007 for the sole purpose of initiating a treatment program for the most difficult to reach drug addicts; this program has been named Chronic Addiction Substitution Treatment (CAST). Currently Inner Change has supported work towards the development of five clinical research trials that will be forwarded to Health Canada for approvals.

The Clinical trials will focus on several drug-using populations in Vancouver and will add to the complement of interventions currently taking place in Vancouver. The five trials being developed include:

1. Integration of HIV treatment and addiction treatment.
This trial will focus on drug users who live with HIV, use stimulants and have poor adherence to HIV treatment. It addresses the issue that intravenous drug users are a high-risk group to acquire HIV and other life threatening diseases, such as hepatitis, endocarditis and tuberculosis, and that in order to address these epidemics in general it is important to work on early detection and offer low-threshold integrated treatments. If drug users are not treated early and effectively, there is a high risk of this group infecting others; effective antiretroviral treatment can suppress the virus and decrease the risk of transmission. Participants will have access to state-of-the-art HIV treatment, psychosocial interventions and will be offered an oral stimulant substitution. The double blind, randomized, placebo-controlled study will look at how effective addiction treatment, combined with HIV treatment, can benefit patients and the community. The sample size for this clinical trial will be 100 individuals.

2. Optimized Opioid Substitution clinical trial.
This trial will focus on those who are addicted to heroin or other opioids and are not satisfied with the existing Methadone Maintenance Treatment (MMT) system. It addresses the range of treatments available: while a range of interventions to address the different needs of patients is necessary, the treatment for heroin or other opioid addictions is more limited than the number of options available to those with other medical conditions. Methadone is the gold standard for opiate substitution treatment and is the cheapest and most available option. Patients need to be retained in MMT for at least one year, to show significant, long-term benefits. In BC, however, only 45% of those who enrol in MMT are retained for one year. This trial will consider substituting several substances that have been used in other jurisdictions for heroin users. They include Polamidon (a form of methadone that has fewer side effects in some patients), slow-release oral morphine (which is allowed for substitution in some countries, including Australia), Suboxone (a combination of buprenorphine and naloxone), and methadone. Psychosocial interventions will be offered all participants. The sample size for this double-blind, randomized clinical trial will be 400 individuals; each of the four trial substances will be given to 100 individuals.

3. Heroin Assisted Treatment vs Hydromorphone, intravenous vs oral administration.
MMT and its increased availability improved the overall quality of the treatment of heroin addiction. About 15-20% of chronic heroin users, however, do not respond well to MMT. This group contributes to the core of inner city problems such a crime and street disorder. In other trials, those with severe physical and mental illnesses showed improvement through Heroin-Assisted Treatment (HAT). HAT requires the long-term provision of injection medication within an expensive, supervised treatment setting. Therefore it is critical to understand the required duration and process of transition to oral medication for those who require HAT. This double-blind, randomized trial will take place in two phases. Phase one will involve randomizing participants into two treatment arms: those in one arm will receive diacetylmorphine (heroin) as part of the treatment regime and those in the second arm will receive hydromorphone (available in Canada as Dilaudid). The second phase of the clinical trial will randomize 50% of each arm to oral routes of administration, to test whether this method of administration can be as effective as injection of these substances. Psychosocial interventions will be offered all participants. The planned sample size is 250.

4. The treatment of stimulant dependence.
This double-blind, randomized, placebo-controlled trial will focus on heavy stimulant users and compare three approaches to treatment: psychosocial, pharmacological and work-focused rehabilitation. In the past decade, the use of cocaine and crystal methamphetamine has grown enormously and led to major problems in North American inner city drug scenes, including the one in Vancouver. Stimulants are used intravenously, orally and smoked, often in combination with other drugs. Heavy users have psychiatric complications and are often involved in a severe level of street crime. The treatment of these patients is especially difficult, because there are few

effective interventions and retention rates in treatment are low. All participants will be offered psychosocial treatment. Participants will be randomized into one of three groups: to receive an oral slow-release amphetamine substitution, a placebo (which will test whether amphetamine substitution has a positive effect on retention in treatment and decreases consumption of psychotropic substances) or an employment-related rehabilitation program. The sample size for this clinical trial will be about 400.

5. Treatment of crack users with contingency management and amphetamine substitution.

The target group for this trial is the less integrated and less treated group of drug users. They are adolescents and young adults who use crack, inject drugs or combine cocaine/crack injection with heroin use. They are often highly marginalized, physically ill and involved in street crime to finance their drug habit. Contingency management refers to a treatment plan that gives rewards for desired changes in behaviour, based on the notion that if a good behaviour is rewarded it is more likely to be repeated. Case management and psychosocial treatment will be offered to all participants, in addition to contingency management, psychoeducational group work and an oral stimulant substitution treatment. The primary outcome that this trial will consider is the level of stimulant use among the participants. This trial will consider a sample of 1,000 individual crack and cocaine users.

These clinical trial proposals are under construction and are in draft form. One Letter of Intent has been submitted to the Canadian Institutes of Health Research (CIHR) and another Letter of Intent for a second trial will be submitted in October. The Inner Change Society has contracted with an executive director to coordinate the research and fundraising efforts for the clinical trials.

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Appendix 2: Substitution Treatment Research Overview

Study/Program	Target Group	Treatment	Main Results	Cost Effectiveness	Conclusion
National Cohort Study 1994-96 Switzerland -	Heroin dependent users who had failed MMT[4]	• Pharmaceutical heroin, • Psycho-social treatment	• decrease in: crime, homelessness, unstable housing, debts, contact with drug scene, street drug use and diseases. • Increase in: good health, employment • Good patient retention rates	• Savings of $15,000Cdn per patient/ year	Since 1999, HAT[5] has been legislated for treatment. Approx. 5% of drug users are enrolled in HAT
RCT[6] 1998-2001 Netherlands	Heroin dependent users who had failed MMT	• Pharm. heroin (injectable,inhalable) • MMT • Psychosoc Tx	• HAT and MMT significantly more effective than MMT alone • 85% of patients who ftransferred at the end of HAT to MMT deteriorated • Good patient retention rates	• HAT and MMT less costly than MMT alone with a mean saving of $19,000 Cdn per patient/ year • Higher program costs compensated by savings in enforcement and property crime	HAT is now part of drug Tx in the Netherlands
RCT 2002-05 Germany	Heroin dependent users who failed MMT and those unreach- able by the system	• Pharm. Heroin • MMT • Psychosoc.Tx	• Improvement in physical and mental health • Decline in cocaine use • A sharp decline in street heroin use • Marked decline of criminal behaviour • An impressive decline in high-risk behaviour like needle sharing, • increase in employment • Good patient retention rates	Not yet evaluated. Preliminary results are in line with Dutch results i.e. HAT is cost-effective despite high costs of Tx	HAT has been recommended to the federal government as a Tx modality and is currently awaiting federal approval
RCT 2003-04 Spain	Heroin dependent users who failed MMT	• Pharm. heroin (injectable) • MMT • Psychosoc. Tx	• Reduced risk behaviour for HIV • Reduced drug related problems • Reduced street heroin use • Improved physical health	Data not available	HAT was safe and more effective than MMT alone for the Tx of MMT resistant patients
RCT Ongoing UK[7]	Heroin dependent users unresponsive to MMT	• Pharm. heroin • MMT, oral & injectable	This is a study of oral vs. injectable methadone as well as injectable methadone vs injectable heroin Resarch aims to examine safety, efficacy and cost effectiveness of Tx with injectable opioid Tx (methadone and heroin) compared to optimised oral methadone treatment An estimated 60% of crime is drug related which is expected to reduce significantly with heroin prescription and that cost savings from crime reduction would outweigh the cost of treatment Results expected in 2008		
RCT Ongoing Canada	Treatment refractory opiate dependent users	• Pharm. heroin • Dilaudid • Methadone	Expected results: Better retention rates, Less illicit drug use and less criminal behaviour with HAT than MMT for treatment resistant users Results are expected in late 2008		
RCT to begin in Belgium Fall 2007					

STIMULANT SUBSTITUTION: SOME EXAMPLES OF RECENT RESEARCH

[4] MMT= Methadone Maintenance Treatment
[5] HAT= Heroin Assisted Treatment;
[6] Randomized Control Trial
[7] The British approach allows for the prescription of heroin to heroin dependent users and amphetamines to stimulant dependent users and has been practiced legally for a few decades. However, no controlled study had been undertaken to test the efficacy of drug replacement treatment until recently.

Many medications have been tested for the treatment of stimulant dependence. Despite this, no single pharmacotherapy has proven effective. Further research in Innovative approaches integrated with psychosocial therapy is warranted.
Below are some examples of significant research and their main results

Study/Program	Target Group	Treatment	Main Results
RCT, 12-week 2001 USA	Cocaine dependent users	• Dextroamphetamine (15-30 mg., then doubled to 30-60 mg after 5 weeks) & PBO[8] • psychosocial therapy for all	• high attrition rates; retention was highest in 15-30mg group • illicit drug use lowest in 30-60mg group
2RCTs 26-wks, 2001 USA	Concurrent cocaine & heroin dependent users	• Dextroamphetamine (15-30 mg., then doubled to 30-60 mg after 5 weeks) & PBO • Risperidone & PBO • Methadone & psychosocial therapy for all	• opioid use reduced in all groups with most reduction with 30-60mg dextroamphetamine • cocaine use reduced most with 30-60 mg- dextroamphetamine, with no reduction in PBO and risperidone • study provides support for dextroamphetamine
RCT 14-week 2003 Australia	Cocaine injectors	• Dextroamphetamine & PBO	• Retention rates same in both groups • Cocaine use reduced with Dextroamphetamine • Criminal activity reduced with Dextroamphetamine • Severity of cocaine dependence reduced with Dextroamphetamine Conclusions recommend a definitive evaluation of Dextroamphetamine as a treatment option
Substit. Program 1994 UK	Amphetamine injectors	• Oral dextroamphetamine • Psycho social Tx	• over 50% stopped injecting, the rest reduced frequency of injecting • 13% became abstinent criminal activity diminished
RCT, 12-week 2001 Australia	Amphetamine dependent, seeking treatment	• Psychosocial therapy for all • Dextroamphetamine (up to 60 mg) for 50% of clients	• Reduced amphetamine use and dependence and injecting behaviour • Reductions slightly higher in dextroamphetamine groups
RCT, 14-week 2007 USA	Cocaine dependent with ADD	• Methylphenidate (MPH) or Ritalin & PBO • Psychosocial Tx	• Results complicated and inconclusive • MPH group improved in ADD symptoms • MPH group decreased cocaine use
RCT 20-week 2006 Finland	Amphetamine injectors	• Methylphenidate, Aripiparazole & PBO • Psycho social Tx	• MPH group showed less iv amphetamine use over PBO group • Aripiparazole group showed more iv amphetamine use over PBO

[8] PBO=Placebo