Do No Harm:
Primum non nocere and Methadone Maintenance Treatment

Executive Summary

The following review of the evidence in support of MMT reveals that, in BC, the most that can be evidenced is that MMT may provide a 20% reduction in crime for 47.7% of its clients while retaining only 41% of its clients in treatment for one year.

More generally, the 2009 Cochrane review concluded that MMT is only effective at retaining individuals in MMT the sole benefit of which is reducing illicit opioid use. They found no other outcome to be statistically significant. The amount of illicit opioid use necessary to be considered a successful reduction is only 20% in BC and the single relevant report shows that only 41% of MMT clients managed that feat. There are no studies which demonstrate any other results for BC's implementation of MMT.

Against these meagre benefits must be weighed the costs.

In British Columbia, we pay at least $67 million dollars to accomplish this minimal reduction in illicit opioid use. The direct costs are likely much higher as the reported figures do not include any ancillary services or drug screening tests.

In BC, methadone clients are shown to be 267% more likely to require hospitalization than heroin users. This finding confirms the likelihood that BC also has a higher death rate for methadone than for heroin. Higher death rates have been confirmed by studies in other jurisdictions.

The sole pharmacological benefit of methadone, preventing withdrawal symptoms from heroin, is replaced with more extended withdrawal symptoms from methadone. All of the deleterious side effects of heroin are shared by methadone.

Assessing the precise costs for the impacts of MMT on the individual clients, for highway users and for children and families has been made impossible by the failure of BC health agencies to track and/or report the relevant statistics. Evidence from other jurisdictions demonstrates that those impacts are negative ones.

MMT is a treatment option for, at most, 10% of persons seeking treatment. Abstinence-based treatment options are appropriate for 100% of substance abuse problems. When the wishes of those seeking treatment are taken into account, MMT becomes, at best, a 2% solution.

While the evidence regarding the actual outcomes of MMT is sufficiently egregious in and of itself, it is made more so by the ready availability of effective, abstinence-based programs which are less costly, provide more certain benefits and avoid more harms.

Occam's razor provides the most useful tool for understanding the absence of BC studies showing any effectiveness for MMT. The most simple explanation is this – MMT simply doesn't work.

Introduction

What follows is an exploration of the Methadone Maintenance Program as it is prescribed by the doctors of British Columbia. (CPSBC 2009) Also discussed is Methadone Maintenance Treatment as that course of pharmacological treatment is delivered by the pharmacists of British Columbia. (CPBC 2013). Both of these programs assert claims to be founded upon sound science and frequently allude to their "evidence based" nature. Accordingly, the studies which underpin those claims, and many others, are also considered.

Methadone Maintenance Treatment has been a part of the addictions response in British Columbia for more than fifty years. Nonetheless, it remains a controversial response to opioid addiction. As recently as 2012, only 2.7% of British Columbia's accredited doctors were prescribing the drug. (PHO 2013).

At the outset it is important to note that methadone has been used to treat opioid addiction in two ways. The original treatment was to use methadone as a substitute opioid by which an addict could be tapered off of their opioid addiction. This form of treatment generally extended for less than a month and was considered a detoxification treatment. Currently, the detoxification use of methadone is deprecated by both the College of Physicians and Surgeons of British Columbia (CPSBC) and the College of Pharmacists of British Columbia (CPBC). The second use of methadone is to replace an addict's drug of choice, typically heroin, with methadone. It is this second usage which is known as Methadone Maintenance Treatment (hereafter referred to as MMT). The stated aims of MMT do not include a cessation of drug use but rather aim to reduce the use of illicit drugs by the addict and the deleterious effects which accompany that use.

It is the thesis of this article that MMT has not been, nor can it be, justified on a cost-benefit analysis. Neither can MMT be justified on the basis of its reducing harms to either the addict or to society at large.

In order to forestall the temptation, and the criticism, of invoking 'straw men' in aid of its main theses, this article takes the less usual approach of quoting liberally from the studies upon which it is based. One thing made patent by this review is that the British Columbia based studies written by proponents of MMT all too frequently make assertions regarding the available evidence which are not actually supported by the studies that they cite. In this article, therefore, the actual words of the underlying studies are frequently and fulsomely quoted.

A Brief History of Methadone

Methadone was developed in 1937 in Germany by scientists working for I.G. Farbenindustrie AG at the Farbwerke Hoechst. They were looking for a synthetic opioid that could be created with readily available precursors. This was in response to an economic embargo by Britain and others which created a morphine shortage in Germany. The reason for its swift abandonment as an alternative to morphine was due to the adverse effects it had on German soldiers during early trials and the availability of other synthetic opioids which they had developed. There was very little military use of the drug during World War II. There was no use of the drug by civil authorities as it was unknown to them. (Gerlach 2004)

After the war, all German patents, trade names and research records were requisitioned and expropriated by the Allies. The records on the research work of the I.G. Farbenkonzern at the Farbwerke Hoechst were confiscated by the U.S. Department of Commerce Intelligence, investigated by a Technical Industrial Committee of the U.S. Department of State and then brought to the US. In 1947, the drug was given the generic name "methadone" by the Council on Pharmacy and Chemistry of the American Medical Association. Since the patent rights of the I.G. Farbenkonzern and Farbwerke Hoechst were no longer protected, each pharmaceutical company interested in the formula could buy the rights for commercial production of methadone for just one dollar. This rather arcane process is the explanation for the extremely low cost of methadone. Pharmaceutical companies do not need to recoup costs of research and development.

Methadone was introduced into the United States in 1947 by Eli Lilly and Company as an analgesic.

> In 1947, Harris Isbell and his colleagues, who had been experimenting extensively with methadone, discovered that methadone was beneficial in the treatment of opiate-dependent patients. Several studies from the United Kingdom in the 1940s described methadone's efficacy in reducing heroin withdrawal symptoms. Ingeborg Paulus and Dr. Robert Halliday, working with the Narcotic Addiction Foundation in Vancouver, established the first methadone maintenance treatment program in the world and published their findings in the Canadian Medical Association Journal in 1967. In the United States, Dr. Vincent Dole and Dr. Marie Nyswander confirmed the feasibility of using methadone as a maintenance medication for heroin dependence. Since then, many other studies have shown the efficacy of using methadone as a maintenance medication for opioid dependence. These studies demonstrate a three- to four-fold increase in death rates in patients discontinuing methadone maintenance treatment. In addition to physical, mental and social health benefits, studies have consistently shown that risk of communicable infection is significantly reduced by participation in methadone maintenance treatment, even in patients failing total abstinence from illicit drugs. (CPSBC 2009)

According to studies which post-date this guidance, most of these claims are not well founded and are discussed below.

Pharmacological Properties

The doctors of British Columbia are provided with the following information by CPSBC.

Pharmacology of Methadone

Methadone is an oral long-acting synthetic opioid which is effective in treating opioid dependence. It is primarily a mu (μ) opioid receptor agonist and when administered in an adequate dose, it will prevent opioid withdrawal, reduce opioid craving and block the euphoric effects of short-acting opioids such as heroin.
Knowledge of the pharmacology of methadone will assist practitioners in avoiding problems associated with overdosing or relapse due to underdosing.

3.1 Absorption
Oral methadone is 80 to 95 per cent bioavailable compared to only 30 per cent for oral morphine.
Methadone is rapidly absorbed following oral administration.

3.2 Duration of action/metabolism
The time to peak plasma concentration and peak clinical effect is 4 hours (range of 2 to 6 hours).
The plasma half-life is extremely variable, averaging 24 to 36 hours at steady state, but ranging from 4 to 90 hours.
As a result of its long half-life, methadone may accumulate, leading to sedation and respiratory depression.
It takes 4 to 5 days for methadone plasma levels to reach steady state.
Methadone metabolism is primarily a function of liver enzyme activity involving cytochrome P450 isoforms. There are many drugs that interact by inducing, inhibiting or acting as a substrate for these enzymes. This can result in clinically significant drug interactions.
Genetic and environmental factors can also act on these enzymes leading to a high degree of variation of individual methadone responsiveness.
...
Methadone is primarily excreted as a inactive metabolite (10 per cent as unchanged methadone) primarily in urine and feces.
Compromised renal function does not preclude the use of methadone.

3.3 Tolerance
Cross-tolerance between methadone and other opioids is unpredictable.
The rate of development of tolerance varies between individuals.
Tolerance to the various effects of methadone develops at different rates. Tolerance to the euphoric effects of methadone develops quickly and may be interpreted by patients as being due to an inadequate dose. Tolerance to respiratory depression is less rapid in onset and tolerance to the autonomic side effects is the slowest.
Tolerance can rapidly be lost upon stopping methadone in as little as 3 days.
The therapeutic treatment window for methadone is short and can be further compromised by concomitant ingestion of alcohol and sedative-hypnotics such as benzodiazepines. (CPSBC 2009)

A more technical assessment is publicly available as a result of the Health Canada approval process. The Product Monograph of Mallinckrodt Canada details the way that methadone acts in the body and its effects. While technical, it is important to recall these various pharmacological aspects while assessing the risks that MMT presents due to its inherent nature.

Physicochemical properties:
Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in METHADOSE as the racemic mixture. ...

Mechanism of Action
Methadone is an opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the κ and σ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of morphine. Like many basic drugs, methadone enters mast cells and releases histamine by a non-immunological mechanism. Similar to morphine, both isomers are 5-HT(3) receptor antagonists, although l-methadone producing greater inhibition than d-methadone. Methadone causes a dependence syndrome of the morphine type. Cross- tolerance between morphine and methadone has been demonstrated, as steady-state plasma methadone concentrations required for effectiveness (C50%) were higher in abstinent rats previously dosed with morphine, as compared to controls.
Some data indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to product neurotoxic effects in animals. Prolongation of the QT interval associated with methadone can lead to potentially fatal ventricular arrhythmias and is caused by block of the rapid component of the cardiac delayed rectifier K(+) current (I(Kr)), which is encoded by hERG related gene. In-vitro effects of methadone have been compared to heroin in human embryonic kidney cells expressing hERG currents, with methadone ex hibiting 100-fold higher potency (IC50 4.8 μM) at inhibiting hERG than heroin (IC50 427 μM).

Pharmacokinetics
Absorption:
Methadone is one of the more lipid soluble opioids, and is well absorbed from the gastrointestinal tract. Following oral administration, the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution:
Methadone undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in lung, liver and kidneys being much higher than in the blood. Methadone is unusual in the opioid class, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to a1-acid glycoprotein (85% to 90%). Marked variations in plasma levels occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms. Methadone is secreted in saliva, sweat, breast milk, amniotic fluid and umbilical cord plasma. The concentration in cord blood is about half the maternal levels.
Metabolism:
Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.
Excretion:
The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life (T1⁄2) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

TOXICOLOGY
In animals, methadone is 3 to 10 times more toxic than morphine, depending on the species, and 2 to 3 times more toxic than meperidine. In acute dose toxicity studies in rats, methadone is about 10 times more toxic than morphine orally, about 6 times more toxic subcutaneously, and about 25 times more toxic intravenously. The l-isomer of methadone, which predominantly accounts for withdrawal suppression activity of the racemic mixture, demonstrates a similar toxicity to that seen with d-l-methadone.

ADVERSE REACTIONS
Adverse Drug Reaction Overview
Heroin Withdrawal
During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.
Initial Administration
The initial METHADOSE dose should be carefully titrated to the individual. Too rapid titration

for the patient's sensitivity is more likely to produce adverse effects.
The major hazards of methadone are respiratory depression, QT interval prolongation and systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred. Patients may be particularly vulnerable during the stabilization period.
The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, constipation and sweating.
Maintenance on a Stabilized Dose
During prolonged administration of METHADOSE, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.
Other adverse reactions include the following: (listed alphabetically under each subsection)
Body as a Whole – asthenia (weakness), edema, headache
Cardiovascular (see WARNINGS AND PRECAUTIONS, Cardiac Conduction Effects) – arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia
Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis
Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis
Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain
Nervous - agitation, confusion, disorientation, dysphoria, euphoria, insomnia, sleep-disordered breathing, seizures
Respiratory – pulmonary edema, respiratory depression
Skin and Appendages – pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria
Special Senses – hallucinations, visual disturbances
Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy
Drug Abuse and Dependence
METHADOSE contains methadone, a potent Schedule I opioid agonist. Schedule I opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.
Abuse of METHADOSE poses a risk of overdose and death. This risk is increased with concurrent abuse of METHADOSE with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.
Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms ...
DRUG INTERACTIONS
Overview: Effects of CYP inhibitors and inducers
In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although anti-

retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, and lopinavir + ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity.
Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.
Drug-Drug Interactions
Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists
As with other μ-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.
Opioid antagonists:
Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see OVERDOSE). Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.
Anti-retroviral Agents
i) Impact on methadone plasma levels
Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination – Co-administration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.
Delavirdine - Dosage of methadone may need to be decreased when co-administered with delavirdine.
ii) Impact on concomitant drug levels, by methadone
Didanosine and Stavudine – Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.
Zidovudine – Experimental evidence demonstrated that methadone increased the AUC of zidovudine which could result in toxic effects.
Antibacterials and Antifungals
Rifampicin - Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary.
Ciprofloxacin - Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Reduced serum concentrations of ciprofloxacin may occur. Concomitant use may lead to sedation, confusion and respiratory depression.
Erythromycin - Theoretically this may increase methadone levels due to decreased methadone metabolism.
Fluconazole and ketoconazole - May raise methadone levels, due to decreased methadone metabolism.
Voriconazole - May raise methadone levels due to decreased methadone metabolism.
Anticonvulsants (Phenytoin, Phenobarbital, Carbamazepine and Primidone):
Induces methadone metabolism with the risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.

Interactions with Alcohol and other CNS depressants
Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory
depression.
Anaesthetics, hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole), anxiolytics, sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly. Antipsychotics may enhance the sedative effects and hypotensive effects of methadone.
Illicit drugs that cause central nervous system depression may increase the general depressant effects of methadone when used concomitantly. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.
Monoamine Oxidase (MAO) Inhibitors
Severe and unpredictable reactions have been reported with concomitant use of MAOIs and opioid analgesics. Since the safety of methadone in this regard has not been established, the use of methadone in patients who have received MAO inhibitors during the previous 14-day period is not recommended. However, if the use of METHADOSE is necessary in such patients, a sensitivity test should be performed in which incremental doses of METHADOSE are administered over the course of several hours while the patient's condition and vital signs are under careful observation.
SSRIs
Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon co-administration with METHADOSE and result in increased opiate effects and/or toxicity.
Desipramine
Plasma levels of desipramine have increased with concurrent methadone administration.
Potentially Arrhythmogenic Agents: Methadone and QT interval prolongation
In patients taking drugs affecting cardiac conduction, or drugs which may affect electrolyte balance, there is a risk of cardiac events when methadone is taken concurrently.
Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with METHADOSE. Pharmacodynamic interactions may occur with concomitant use of METHADOSE and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.
Caution should also be exercised when prescribing METHADOSE concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.
Histamine H2 Antagonists
Histamine H2 antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.
pH of urine
Drugs that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.
Others
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.

Grapefruit Juice
Pharmacokinetic studies show that concomitant grapefruit can cause a modest increase in methadone plasma levels. The clinical relevance of this is unknown.
Drugs affecting gastric emptying
Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.
Mexiletine (antiarrhythmic)
Methadone delays the absorption of mexiletine.
Drug-Herb Interactions
St. John's Wort
Administration of METHADOSE along with other CYP3A4 inducers may result in withdrawal symptoms.
Drug-Laboratory Interactions
Pregnancy Tests
Methadone may interfere with urine testing for pregnancy. (Mallinckrodt Canada 2013)

The understanding of the pharmacological aspects and impacts of methadone can now be applied to understand how it is being used.

The Claims for MMT in British Columbia

The CPBC have set out for their pharmacists the following:

> Opioid dependence is a health concern with implications for the individual patient as well as the public. Methadone maintenance treatment is recognized internationally as among the most effective treatments for opioid dependency. Addiction treatment experts recommend that methadone treatment for opioid dependence be delivered with a maintenance-oriented, rather than abstinence-oriented, philosophy. This approach acknowledges opioid dependence as a chronic disease.
> Many studies, conducted over several decades in different countries, have clearly demonstrated that the effective delivery of methadone maintenance treatment reduces non-medical opioid use, other problematic substance use, criminal activity, mortality, injection-related risks and transmission of blood-borne disease. Additional positive results are improvement in physical and mental health, social functioning, quality of living and pregnancy outcomes.
> Methadone, a long-acting, orally effective opioid, is used as a substitute for heroin or other narcotics when treating opioid dependence. Methadone eliminates withdrawal from and reduces cravings for, opioids. Methadone does not produce euphoria, and it blocks the euphoric effects of other opioids. When used in the treatment of opioid dependence, a single oral dose of methadone is effective for at least 24 hours. Eventual withdrawal from methadone is not necessarily the goal of the program, although some individuals may work with their physician and pharmacist to decrease their dose and eventually stop using methadone. (CPBC 2013)

Another British Columbia author has made the following observation:

> As opioid dependence is commonly recognized as a chronic disease, the philosophy behind methadone substitution treatment is meant to be maintenance-oriented rather than abstinence-oriented. (Reist 2010)

The CPSBC has also made particular note of the chronic, relapsing nature of opioid addiction.

> Opioid dependence is a chronic, recurrent medical illness associated with co-morbid mental illness, transmission of infectious diseases (such as HIV/AIDS and hepatitis C), and premature mortality. Methadone maintenance is widely regarded as both a highly effective treatment for opioid dependence and an evidence-based harm reduction intervention to prevent the transmission of blood-borne pathogens. Additionally, numerous studies have found that methadone maintenance reduces harms associated with non-medical opioid use, including injection-related risks and criminal activity, and increases the social functioning and quality of life of patients. (Provincial Health Officer 2013)

A full discussion in respect of these various claims is found below. However, at this point it is fundamentally important to observe the importance to an effective MMT of incorporating services beyond simply prescribing methadone.

> Components [of best practice]
> - methadone;
> - medical care;
> - other substance use treatment;
> - counselling and support;
> - mental health services;
> - health promotion, disease prevention and education. (Health Canada 2002)
>
> Most methadone patients struggle with a number of challenges, such as poverty, lack of education, exposure to violence, poor nutrition, serious physical or mental health problems and involvement with the criminal justice system. These problems do not disappear just because the patient receives a daily dose of methadone. (CPSBC 2009)
>
> Methadone programs should be more than a simple dispensing of methadone prescriptions: they should incorporate a comprehensive biopsychosocial and spiritual approach to help patients cope with their problems. (CPSNS 2012)
>
> Methadone as maintenance clearly has its detractors, but coupled with adequate psycho-social supports and counselling (some of it of the kind provided in many otherwise abstinence-based programs), it is for many heroin-dependant persons the most effective treatment available. (Kendall 2013a)
>
> The effectiveness of the province's Methadone Maintenance System depends on a multidisciplinary approach with three key components: prescribing, dispensing, and counselling or other adjunct services and supports.

...

A 2010 review of methadone maintenance in BC identified the delivery of the psychosocial services component as one of the system's biggest challenges. Psychosocial services and supports are an integral part of methadone maintenance and are provided by health authorities, private physicians, counsellors, and other allied health professionals. (Provincial Health Office 2013)

The Evidence of the Claims for MMT in British Columbia

Claim: 0pioid dependence is a chronic, relapsing disease.

This claim is largely non-controversial. It is entirely true that persons who have an addiction to opioids tend to relapse from periods of any kind of treatment. It is also true that opioid addiction is chronic in the sense that it is a continuing condition. This can be understood best by considering an acute condition. In the latter, for example a bacterial infection, once treated the condition is eradicated. In a chronic condition, such as diabetes, treatment provides relief and health benefits but does not eradicate the underlying condition.

The claim as advanced by proponents of MMT becomes problematic when it is made as if it solely relates to opioid dependence. In fact, all addictions are chronic, relapsing conditions. Whether considering tobacco, alcohol, cocaine, any other drug or gambling, addicts suffer a chronic condition which tend to cause them to relapse.

In respect of tobacco, the Ontario Tobacco Research Unit has found that, on average, a person requires 30 attempts before they successfully able to quit smoking. Their studies also establish that the proportion of the Canadian population that now smokes is about 20% having plummeted from the 80% fifty years ago.(OTRU 2013) This level of success has been in relation to nicotine which is consistently rated as the most difficult of drugs to quit. (Kozlowksi 1989, Henningfield, 1998)

1 = Most serious 6 = Least serious

HENNINGFIELD RATINGS

Substance	Withdrawal	Reinforcement	Tolerance	Dependence	Intoxication
Nicotine	3	4	2	1	5
Heroin	2	2	1	2	2
Cocaine	4	1	4	3	3
Alcohol	1	3	3	4	1
Caffeine	5	6	5	5	6
Marijuana	6	5	6	6	4

BENOWITZ RATINGS

Substance	Withdrawal	Reinforcement	Tolerance	Dependence	Intoxication
Nicotine	3*	4	4	1	6
Heroin	2	2	2	2	2
Cocaine	3*	1	1	3	3
Alcohol	1	3	4	4	1
Caffeine	4	5	3	5	5
Marijuana	5	6	5	6	4

*equal ratings

As we have been successful in getting people to eventually quit smoking, logic would suggest that we should also make continuing efforts to assist opioid addicts to quit. However, as demonstrated by the North American Opiate Medication Initiative (NAOMI) trials, BC harm reductionists are prepared to place opioid addicts on life long opioid substitution therapies with as little as a single relapse.

To extend the tobacco analogy, one needs only consider the level of evidence that would be necessary to justify shifting a nicotine addict from smoking cigarettes to chewing tobacco. The problem of addiction and the related poor health outcomes is derived from the inherent nature of the drug and not to the manner nor the vehicle of its ingestion. Moving the heroin-dependant addict to methadone makes just as little sense as moving the crack cocaine addict to the practice of snorting cocaine. Just as ridiculous would be treating a gambling addiction by moving the addict away from the slot machines and over to the blackjack table. And yet that is precisely what MMT does for the opioid addict.

Put simply substitution therapy is not effective, nor is it condoned, for any other chronic relapsing disease.

Claim: MMT reduces non-medical opioid use

Again, this claim is largely uncontroversial. The lack of controversy lies in the simple understanding that MMT is aimed at replacing illicit heroin with licit methadone.

Where concerns arise is the degree to which illicit opioid use is actually reduced. In the sole report in respect of BC's MMT, participants were considered as having reduced their illicit drug use if it fell by 20%. That study does not differentiate between illicit opioid and other illicit drug use. The study documents that only 42.1% of the MMT participants achieved the 20% reduction in illicit drug use. The converse is equally true. That is, more than half of the MMT clients failed to reduce their illicit drug use by 20%.

+Illustration 1: Source: Olviedo-Joekes 2009

Table 2. Primary Outcomes at 12 Months.*

Variable	Methadone (N=111)	Diacetylmorphine (N=115)	Rate Ratio (95% CI)	P Value
	number (percent)			
Reduction in illicit-drug use or other illegal activities	53 (47.7)	77 (67.0)	1.40 (1.11–1.77)	0.004
Reduction in illicit-drug use alone	15 (13.5)	26 (22.6)		
Reduction in other illegal activities alone	6 (5.4)	1 (0.9)		
Reduction in both illicit-drug use and other illegal activities	32 (28.8)	50 (43.5)		
Retention in addiction treatment	60 (54.1)	101 (87.8)	1.62 (1.35–1.95)	<0.001
NAOMI diacetylmorphine	NA	77 (67.0)		
NAOMI methadone maintenance treatment	45 (40.5)	21 (18.3)		
Other methadone maintenance treatment	13 (11.7)	2 (1.7)		
Other, nonmethadone treatment	0	0		
Abstinence	2 (1.8)	1 (0.9)		

* Rate ratios are for the diacetylmorphine group as compared with the methadone group. NA denotes not applicable, and NAOMI North American Opiate Medication Initiative.

The same study further demonstrates the limits of methadone's effectiveness. As seen in the graphic below, methadone only reduced the use of illicit heroin by roughly one-half in terms of the number of days of illicit heroin use.

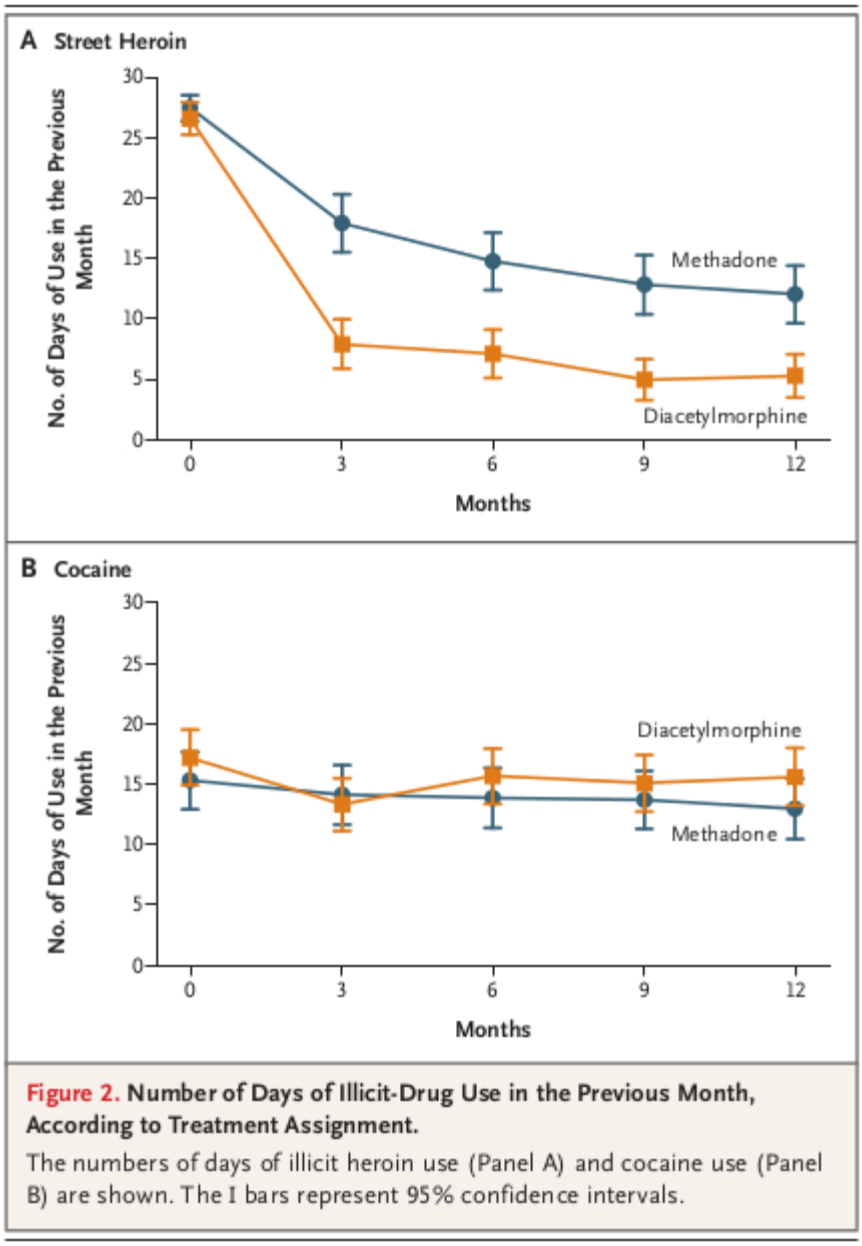


Figure 2. Number of Days of Illicit-Drug Use in the Previous Month, According to Treatment Assignment.

The numbers of days of illicit heroin use (Panel A) and cocaine use (Panel B) are shown. The I bars represent 95% confidence intervals.

Illustration 2: Source: Oviedo-Joekes 2009

Taken together, the evidence is that in BC MMT, 42.1% of clients may reduce their illicit heroin use by an average of roughly 50%. The study is silent as to the use of other illicit opioid use.

Claim: MMT reduces other problematic substance use.

As seen in Illustration 2 above, the sole BC evidence in relation to this claim demonstrates that MMT has virtually no effect on the concurrent use of cocaine. Unfortunately, there appear to be no BC reports of the use of drugs other than cocaine.

The continuing use of other problematic substances is such a problem for all MMT programs that there are a number of studies which report attempts to provide monetary incentives for sustained abstinence from non-opioid drugs. The results of one of those studies are presented below.

Table 4. Samples Submitted That Tested Negative for Drug

Drug	Incentive Group (n = 198)*	Usual Care Group (n = 190)*	OR (95% CI)†
Primary target			
Stimulants only	54.4	38.7	1.89 (1.35-2.63)
Alcohol only	99.1	98.7	1.43 (0.58-3.45)
Secondary			
Opioids	71.4	62.4	1.49 (1.09-2.08)
Marijuana	91.8	90.0	1.25 (0.73-2.17)

Abbreviations: See Table 3.
*Data are given as percentage of each group.
†A generalized estimating equation was used to obtain ORs; the reference is the usual care group.

Table 5. Participants With Specified Weeks of Continuous Stimulant- and Alcohol-Negative Samples

Time, wk	Incentive Group (n = 198)*	Usual Care Group (n = 190)*	OR (95% CI)†
≥4	23.7	9.0	3.1 (1.7-5.7)
≥8	16.7	2.1	9.3 (3.2-26.7)
12	5.6	0.5	11.1 (11.4-86.5)

Abbreviations: See Table 3.
*Data are given as percentage of each group.
†Each analysis was conducted separately; the reference is the usual care group.

Illustration 3: Source: Peirce 2006

Three observations can be made from this study and its data. The first is that 'usual care' group received a course of treatment which included ancillary services such as counselling which are not typically present for BC MMT clients. Therefore, it should be understood that the reported results of this study will be greater than would be expected of a program without those supports.

The second observation is that at least one illicit drug use was demonstrated in 61.3 to 100% of samples from the usual care group with alcohol being largely absent. The financial incentives offered in this study reduced the level of such samples to a minimum of 45.6%.

The third observation is that of the clients from the usual care group, only 0.5% demonstrated 12 weeks of abstinence from illicit drugs. 2.1% of the usual care group attained 8 weeks of abstinence. Less than 10% were able to demonstrate 4 weeks of abstinence over the course of the study. Each of those rates was raised by the availability of a financial incentive. Peirce describes that increase as follows.

> For an approximate direct cost of $1.42 per day, plus urine test costs, the incentive procedure doubled the odds that participants would submit stimulant-negative urine samples and tripled the odds that participants would attain at least 4 weeks of sustained stimulant abstinence. (Peirce 2006)

Another way of describing this result is that, even with financial incentives, 3 out of 4 of the study participants failed to sustain four weeks of stimulant free samples.

Claim: MMT is more effective than non- pharmacological approaches in retaining patients in treatment.

The most current evidence for this claim comes from the 2009 Cochrane review which states:

> Methadone appeared statistically significantly more effective than non- pharmacological approaches in retaining patients in treatment... (Mattick 2009)

This claim also finds support in a 2005 study:

> These findings confirm that MMT at appropriate doses is the most effective in retaining patients in treatment...(Amatoa 2005)

Both of these studies emphasize the importance of substantial ancillary services which are lacking in the BC MMT approach.

As seen in Illustration 1 above, one BC study demonstrates that 54.1% of clients can be retained in MMT in BC. However, that study uses a rather generous basis for determining retention and actually takes credit for clients retained by other programs.

> The first primary outcome was retention in addiction treatment at 12 months (defined as receipt of the study medication on at least 10 of the 14 days before the 12-month assessment, or confirmation of retention in any other treatment program or abstinence from opioids during this interval). The second primary outcome was reduction in illicit-drug use or other illegal

> activities. ...patients were considered to have a response at 12 months if they had an improvement of at least 20% from the baseline score for illicit-drug use or legal status (or both). (Oviedo-Joekes 2009)

The more recent and more general review by the BC Provincial Health Officer has determined that MMT retains 41% of its participants after one year.(PHO 2013).

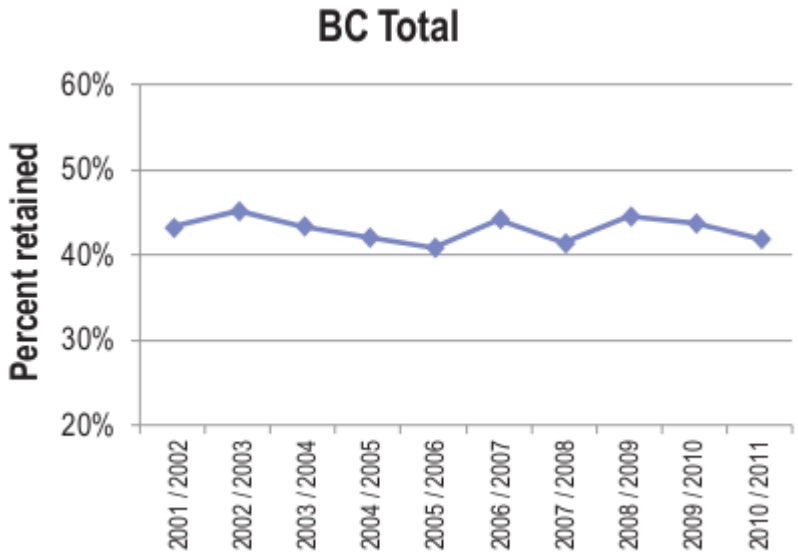


Illustration 4: Source: PHO 2013

When one recalls the discussion above as to the minimal extent of behavioural change that actually occurs during MMT, there is very limited utility in retaining clients in that treatment.

The poor retention rates in BC lead to even less effectiveness of MMT in subsequent episodes of treatment.

> Specifically, the data show that repeat episodes of treatment are of shorter duration than the initial episodes. While it may be that these shorter second, third, and later episodes of treatment lead to stability and recovery, clinical experience suggests that this may not be the scenario. If this interpretation is correct, efforts to retain patients when they first appear for treatment are necessary if patients are to derive the full benefits of MMT. (Strike 2004)

The failure to retain participants within MMT has one, very final, outcome.

> Discontinuation of MMT is associated with a three- to four-fold increase in death rates . Reist 2010

Claim: MMT reduces criminal activity, reduces mortality rates, reduces rates of injection-related risks and transmission of blood-borne disease and provides additional positive results in physical and mental health, social functioning, quality of living and pregnancy outcomes.

The 2009 Cochrane report makes the following statements.

> Methadone appeared statistically significantly more effective than non- pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56- 0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12- 1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10- 2.39)
>
> In addition, it is important to recognise that methadone treatment in these trials was often provided with substantial ancillary services. These ancillary services have included counselling, psycho-social services, medical services and often psychiatric care. The quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment. The extent that clinical programs move away from such an approach might be expected to impact on the effectiveness of methadone. This does not imply that methadone maintenance treatment will become ineffective. Even allowing for some reduction in effectiveness when methadone is not provided in the fashion that it has been in the clinical trials, it is still likely to be effective. The effects of methadone may be modest, if they are judged by unrealistic expectations of patients can easily achieve enduring abstinence from opioid drugs. (Mattick 2009)

Given the actual results being obtained in BC, 'modest' would be a generous manner by which to describe those results. Those results, however, are entirely understandable given the absence of ancillary services necessary to achieve the results reported by Mattick.

A second study highlights that the preponderance of evidence does not support the claim of extended benefits of MMT.

> These findings confirm that MMT at appropriate doses is the most effective in retaining patients in treatment and suppressing heroin use but show weak evidence of effectiveness toward other relevant outcomes. Future clinical trials should collect data on a broad range of health outcomes and recruit participants from heterogeneous practice settings and social contexts to increase generalizability of results. (Amatoa 2005)

Notably, the challenge of Amatoa to collect data demonstrating the broader benefits of MMT has not been met in the intervening years.

In another Canadian study, the absence of an effect on offending rates has also been noted.

> ... the results did not indicate any meaningful differences in the new offence rates between the two groups. (Johnson 2001)

The conclusions of the 2009 Cochrane review as set out above (Mattick 2009), are of particular

relevance because they have been ignored by BC methadone proponents. In the Qualitative Analysis of BC's MMT, Parkes says:

> Several Cochrane Reviews conclude that MMT is effective in treating addiction to heroin and other opioids. (Parkes 2010)

She then cites two Cochrane studies from 2003 and 2004 and fails entirely to note the 2009 findings. It is also instructive to note that her 2010 report does not make a single mention of outcomes or success factors nor, indeed, any objective measure of BC's MMT in the entire report.

Parkes repeated the same disingenuous statement in 2011.

> Several Cochrane reviews have concluded that methadone treatment is effective in treating addiction to heroin and other opioids (Faggiano, et al, 2003: Mattick et al, 2003) MMT has been implemented as a means of addressing a range of health, social harms associated with opiate addiction, including costs related to these harms (i.e. health and criminal justice). Parkes 2011.

The repeated failure to note the conclusions of the 2009 Cochrane review must serve to undermine Parkes' purposes.

What is BC Doing?

It is difficult to come to objective conclusions regarding the actual results of MMT in BC. In no small part, this difficulty is explained by the refusal of health officials to share the data.

> Follow up contact either through phone or email was initiated after 4 weeks of sending out the surveys. Unfortunately, Interior Health and adult addiction services for Vancouver Island Health Authority choose not to participate this year because they submit information to the Ministry of Health Services (MoHS) directly in regard to addiction treatment utilization rates through the existing Addiction Information Management System (AIMS). Attempts were made to access AIMS information directly from the MoHS but unfortunately, due to inconsistent reporting by agencies and health authorities, the ministry is not releasing AIMS information to internal or external researchers. Information contained within the AIMS database suffer many issues with data completion as many departments within the different health authorities have varying mandates in regard to submitting information to AIMS. (Chow 2010)

Nonetheless, Statistics Canada has reported that BC trails the Canadian average on a number of measures relating to mental health and addictions.

- British Columbians are 10% worse off than Canadian average for 'mood disorders'
- British Columbia rate for heavy drinking is 15.8 versus 17.3 for the rest of Canada
- The mental illness hospitalization rate/100k in BC is 594 while the average across Canada is 467
- The mental illness days in hospital/10k in BC is 734 while the average across Canada is 678 (Statistics Canada 2013)

These measures suggest that there may be wider issues with the delivery of mental health and addictions treatment in British Columbia.

More alarming are statistics related to methadone itself.

> 0.145721605060456 rate per 100k hospitalizations by overdose from methadone in 2002
> 0.308429188635914 rate per 100k hospitalizations by overdose from methadone in 2009
> 0.115426443873079 rate per 100k hospitalizations by overdose from heroin in 2009
> (Vallance 2011)

These figures demonstrate that there was 211% increase in methadone hospitalizations since 2002. This also means that by 2009 a citizen of British Columbia was 267% more likely to be hospitalized due to methadone than heroin. Disappointingly, Vallance did not separately report the death rates in respect of methadone and heroin for the same period of time.

As the Provincial Health Officer reported in 2013, the actual number of deaths due to methadone increased fivefold from 2002 to 2011. At the same time, the actual number of methadone users increased by only 79%. Taken together those two figures approximate the increase in hospitalizations

as reported by Vallance.

The Provincial Health Officer provided the following explanation of the increase in deaths.

> Although the number of patient deaths has increased between 2001/2002 and 2011/2012 (reflecting overall growth of the patient population during this period), the rate per 100 person years on methadone has decreased (see Table 2 and Figure 14). These unadjusted rates cannot be used to draw conclusions about the effectiveness or risks of methadone maintenance therapy. However, Figure 13 shows that the number of patients engaged in methadone maintenance increased without a proportional increase in rates of death, providing some reassurance of the relative safety of methadone maintenance in BC. (PHO 2013)

Figure 13. **All-cause Mortality During Methadone Maintenance Treatment, by Fiscal Year, BC, 2001/2002 to 2011/2012**

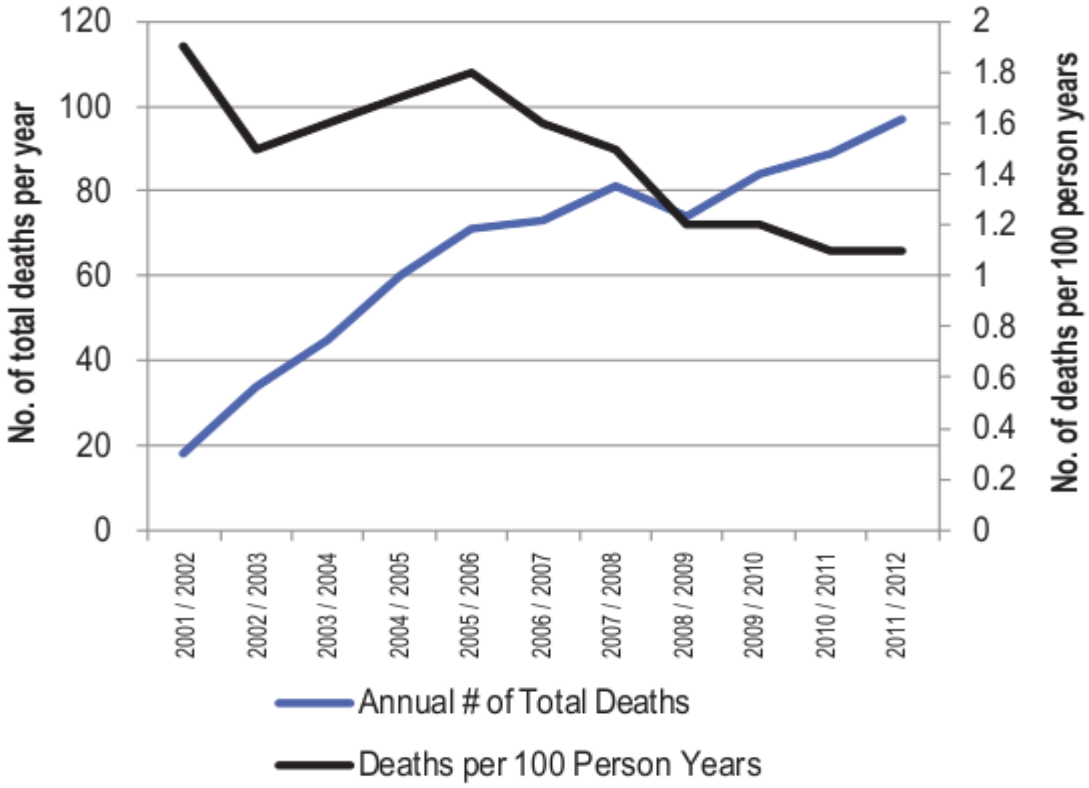


Illustration 5: Source PHO 2013

There is no explanation provided as to how the rate per 100 person years is derived. The absolute

numbers involved are that there appear to have been 18 deaths in 2001/2002 from approximately 7,760 MMT clients. This is a rate of 0.23 %. In 2011/2012, the number of MMT clients rose to 13,894 while the absolute number of deaths appears to be 98. This yields a rate of 0.72%. The threefold increase in death rate is remarkably consistent with the increased rate in hospitalizations reported by Vallance. How the PHO turned those increases into a reduced rate requires a mathematical imagination beyond that possessed by this author. Moreover, a claim to reduced death rates for methadone flies in the face of all the uncontroverted evidence from other jurisdictions which is considered below.

It appears that other relevant data are missing. What would be relevant is whether the mortality rate is higher or lower than heroin users. Also relevant would be the relationship to the general population mortality rates. Both the US and the UK have statistics which demonstrate that the mortality rate is higher on methadone than when using illicit heroin. The further significant data that are missing relate to the number of deaths attributable to methadone where the deceased was not part of the MMT. This would be a useful measure of the degree of diversion. Such a figure would, as well, show the degree of mortality risk transfer that is going on, ie: to children. Inquiries with the BC Coroner's Service reveal that separate statistics are not currently kept by their office as regards to methadone.

There has been an anti-intuitive decrease in the participation rates of physicians in BC.

> In 2011/2012, there were 11,980 professionally active physicians in British Columbia. Of these, 433 were authorized to prescribe methadone for maintenance purposes, and 327 actually prescribed for patients during that 12-month period, 168 (51 per cent) of whom were based in Vancouver Coastal Health Authority. (PHO 2013)

Interestingly, given a 79% increase in MMT clients from 2001/2002 to 2011/2012, the actual number of physicians prescribing methadone has fallen from approximately 410 to approximately 330. This result can be interpreted to mean that there has been a 20% reduction in the number of health professionals who think that MMT might work. That interpretation is consistent with the fact that only 2.7% of physicians believe in methadone enough to prescribe it.

Contrary to the trend with physicians, pharmacies involvement has escalated far beyond the rate of increase in the number of MMT patients. The number of BC pharmacists and pharmacies dispensing methadone for maintenance purposes has more than doubled since 2001/2002. The significance of the rise in both pharmacists (from 875 to 2576 = about a 295% rise) and pharmacies (from 276 to 658 = 238% rise) is that there was only a rise of 79% in patients. This is indicative of the lucrative nature of MMT for pharmacists.

> The total pharmacy costs for methadone maintenance in BC reached nearly $46 million in 2011/2012, $40 million of which was paid by PharmaCare. (PHO 2013)

The $46 million figure is difficult to reconcile. The following average figure of $3301 is predicated on 13,894 patients. However, given only a 41% retention, the relevant figure should be expressed in patient days of treatment.

In BC. pharmacists are paid two cents per mg for an average 100mg dose which is $2 per methadone ingestion. They also receive a once a day dispensing fee which averages $10 (methadone is likely higher but relevant figures aren't publicly available). Pharmacists also receive a further $7.50 for each

witnessed ingestion. At a minimum, the dispensing of each witnessed dose of methadone costs about $19.50 a day. (This probably averages out a little low given the low rate of 'carries' and the higher rate of multiple daily doses). This means that each MMT patient should cost about $7117.50 per year (19.50*365) solely for the cost of methadone and dispensing. If all 13,894 MMT clients were retained for a full year, the annual payments to pharmacies would be $98,890,545.

The direct costs for MMT are reported by the Provincial Health Officer to be:

- $46 million - drugs/dispensing
- $12 million - doctors fees
- 2.37 million – Ministry of Social Development (PHO 2013)

Thus MMT costs British Columbia residents a minimum of $60.37 million per year. However, there are no costs provided for the ancillary services which are required in order to make MMT effective. The absence of costs for ancillary services may be due to their absence from BC MMT, a desire to under-report the cost of MMT or a combination of both of those factors.

The Qualitative Analysis of BC's MMT makes the following observation regarding costs.

> Funding for MMT in BC is multi-faceted and complex. The system is supported by significant expenditures through the Medical Services Plan (e.g., payments to physicians and urine drug screens), BC PharmaCare (e.g., dispensing and drug costs), health authorities (e.g., counselling services), the Ministry of Health Services contract with CPSBC, the Ministry of Housing and Social Development alcohol and drug treatment supplement, and the Health Canada non-insured health benefits program. On top of this, some clients are required to pay up to $80 per month in user fees. (Parkes 2010)

It is instructive to observe how the relevant numbers are reported in Ontario.

> The database consisted of 9479 unique patients. The average age on the date of the first recorded visit was 34.3, and among the patients 62.3% were male. There were 6,425,937 patient days of treatment and the total cost of all treatment-related services was approximately $99,491,000. The total cost was comprised of physician billing (9.8%), pharmacy costs (39.8%), methadone (3.8%), and performing urine toxicology screens (46.7%). The average cost per day for treatment was $15.48, corresponding to $5651per year if patients were to remain in treatment continuously. (Zaric 2012)

The Provincial Health Officer has stated:

> Greater access to methadone maintenance, along with other harm reduction initiatives, has helped contribute to the lower incidence of HIV infection among people who inject drugs. (PHO 2013)

There is no data in that report that ties MMT to any outcome related to the prevalence of HIV infection. However, the Provincial Health Officer also goes on to state:

> An important caveat for this section is that the outcome measures were obtained without an

> attempt to isolate the effect of methadone maintenance (versus no treatment or other treatments). Therefore, the material presented here is intended to be hypothesis-generating and may initiate further analysis of more specific outcomes using observational study designs. (PHO 2013)

This seems to be saying that they have no evidence that the outcomes are related to MMT, or to what degree they may be related or whether they are better or worse than no treatment or any other treatment.

Elsewhere, the Provincial Health Officer has stated:

> MMT programs may be affecting the transmission of HIV among IDU in BC. (Kendall 2011)

This latter statement is consistent with the Qualitative Analysis of MMT in BC where it states:

> The original goals for the rapid expansion of BC‘s MMT program in the 1990s were public health goals, particularly the mitigation of the HIV epidemic in Vancouver‘s Downtown Eastside. While MMT may have contributed to preventing many more HIV infections in BC over the past decade (Anderson, 2000), many former or current injection drug users in the province are currently living with HIV or hepatitis C. There are systemic problems with ensuring consistent linkage between MMT and HIV treatment. (Parkes 2010)

The literature scan from which this article arises revealed what may be a new use of methadone. Curiously, within days anecdotal evidence was received that this practice has taken root in British Columbia. As noted at the outset, methadone has been used both as a detoxification treatment and as a maintenance treatment. During the literature review, however, a few references were found which refer to the practice of placing abstinent former opioid addicts on methadone as a prophylactic measure in anticipation of an imminent relapse to opioid use. From a purely pharmacological approach, such a practice is not a relapse prevention measure, it is, in fact, relapse.

As bizarre as the use of methadone as relapse prevention may seem, the author is now aware of three recent occasions where exactly those actions were taken in BC.

The practice of placing people who are not current opioid users on methadone may not be as rare as logic would dictate. As the graphic below makes clear, the Nova Scotia MMT has almost 40% of its clients start MMT in the absence of opioids appearing in their admission drug screen.

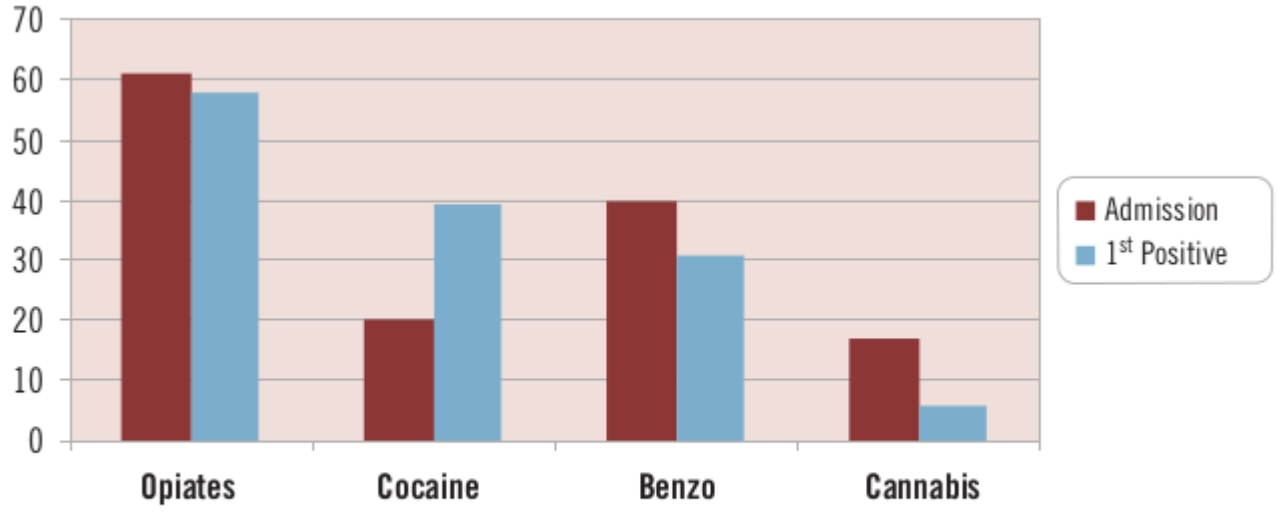


Figure 9. Admission and First Positive Urine Test Jan. 1 – Dec. 31, 2002.

Illustration 6: Source: Francis 2002

Evidence of Methadone's Costs

We have now obtained an understanding of the evidence that supports the benefits that have been attached to MMT. In order to undertake an informed cost-benefit analysis, it is now necessary to understand the range and extent of the costs which also accompany MMT in BC.

The costs of methadone can be appreciated from two perspectives in the same manner as its putative benefits. The first is that of the individual MMT client. The second is the perspective of society at large.

That methadone's dangers are both unique and significant is best illustrated by the extraordinary measures taken to control access and use of the drug. These measures are also a proxy to demonstrate that those dangers are well known in the medical and pharmaceutical communities.

> Methadone prescribing is controlled by both federal and provincial legislation, as well as administrative procedures and guidelines.
> Physicians are required to obtain a special exemption to prescribe methadone for opioid dependence. In BC, the College of Physicians and Surgeons of BC (CPSBC) administers the exemption process to enable specific physicians to prescribe methadone for maintenance treatment. To obtain an exemption to prescribe methadone, physicians must complete a one-day training program and mentor with another methadone-prescribing physician. Methadone maintenance treatment exemption is separate from the exemption to prescribe methadone for pain. Some physicians are exempted to prescribe methadone for both indications.
> Registered pharmacists are permitted to purchase and dispense methadone without federal exemption. However, the College of Pharmacists of BC's (CPBC) Professional Practice

Policy (PPP-66) – Methadone Maintenance Treatment requires that the pharmacy manager and all staff pharmacists employed in a community pharmacy that provides services related to methadone maintenance treatment complete the CPBC's training program and any subsequent updates. You must log into eServices to complete the "Declaration of Completion and Understanding" prior to providing methadone maintenance treatment services. (CPBC 2013)

There are no other prescribing and dispensing regimes like those described above. There is no other drug for which special training and certifications are required both to prescribe and to dispense. The level of danger necessary to require such measures needs to be borne in mind when an assessing the level of benefit that MMT provides.

Even with such extraordinary measures in place, the statutory control measures have proven ineffective. The degree to which they are ineffective has been neatly summarized by a proponent of MMT. As seen in the illustration below, Urban Health Research Initiative (UHRI) has found that approximately 40% of the persons in their study cohort state that they can acquire prescription methadone illicitly within 10 minutes of desiring to do so.

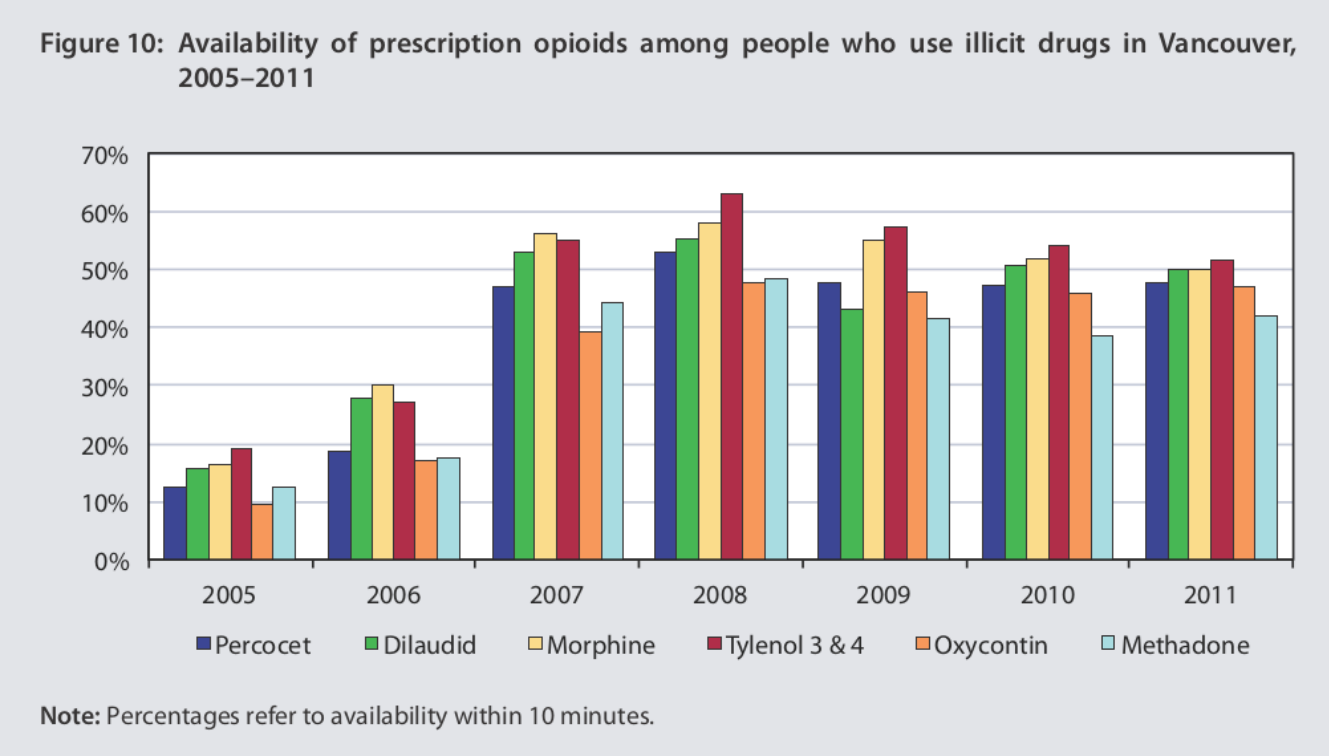


Illustration 7: Source: UHRI 2013

Just as disturbingly, the respondents of that study demonstrate that the unique methadone control regime is not significantly more, or less, effective than the less encompassing measures taken in respect of other opioids.

The US has demonstrated the same failure of their control measures regarding methadone.

> DEA data suggest that abuse of methadone diverted from its intended purpose has also contributed to the rise in overdose deaths as the number of methadone drug items seized by law enforcement and analyzed in forensic laboratories increased 262 percent, from 2,865 in 2001 to 10,361 in 2007. (GAO2009)

Costs to Individuals MMT Clients

To understand the costs to individuals in MMT, recall that the only pharmacological benefit is the prevention of withdrawal symptoms from heroin. While those acute withdrawal symptoms cause immense discomfort for up to 7 days, there are no reports of anybody ever dying from opioid withdrawal.

> Unlike alcohol and sedative withdrawal, uncomplicated opioid withdrawal is not life-threatening. (CDC 2012)

In considering the long term side effects of methadone, the words of Norwegian researchers are important to recall.

> Since the mid-1960s, methadone has been used to treat heroin addiction. This is considered to be a successful treatment but, despite extensive and prolonged use, little is known about possible side effects. There are large knowledge gaps in this field. (Andersen 2012)

The individual that moves from heroin to methadone actually makes their situation worse. While anecdotal reports of methadone withdrawal are somewhat subjective, the extended length of methadone withdrawal cannot be questioned.

> All opioid agents produce similar withdrawal signs and symptoms with some variance in severity, time of onset, and duration of symptomatology, depending on the agent used, the duration of use, the daily dose, and the interval between doses. For instance, heroin withdrawal typically begins 8 to 12 hours after the last heroin dose and subsides within a period of 3 to 5 days. Methadone withdrawal typically begins 36 to 48 hours after the last dose, peaks after about 3 days, and gradually subsides over a period of 3 weeks or longer. (SAMSHA 2009)

One of the side effects which is frequently reported by former MMT patients is loss of calcium and consequent bone pain and more frequent fractures. This side effect has been confirmed.

> In summary, the majority of individuals examined in this methadone maintenance treatment program had low BMD[bone mineral density]. (Kim 2006)

The loss of calcium will be exacerbated by continued heroin use and being HIV positive. (Sharma 2010)

Two further observations regarding side effects are important. The first is the sheer number of adverse reactions that can be expected of drug interactions with methadone.

> As the tables in this document indicate, there are more than 100 substances – medications, illicit drugs, OTC products, etc. – that can interact in some fashion to affect a patient's response to methadone. Leavitt 2005

Two of the groups of drugs that are contraindicated are those which are used to treat depression and other mood disorders and those drugs used to treat HIV.. These, of course, are the very conditions which predominate among addicts.

The greatest danger to MMT clients is death.

As noted above, methadone deaths have increased by 500% in British Columbia among MMT clients while the number of clients has only increased by 79%.

This phenomenon exactly matches what is occurring in both the US and the UK.

> Methadone contributed to nearly 1 in 3 opioid pain reliever (OPR) deaths in 2009. Yet only 2% of OPR prescriptions are for methadone. About 5,000 people die every year of overdoses related to methadone. Six times as many people died of methadone overdoses in 2009 as died in 1999. (CDC 2012)

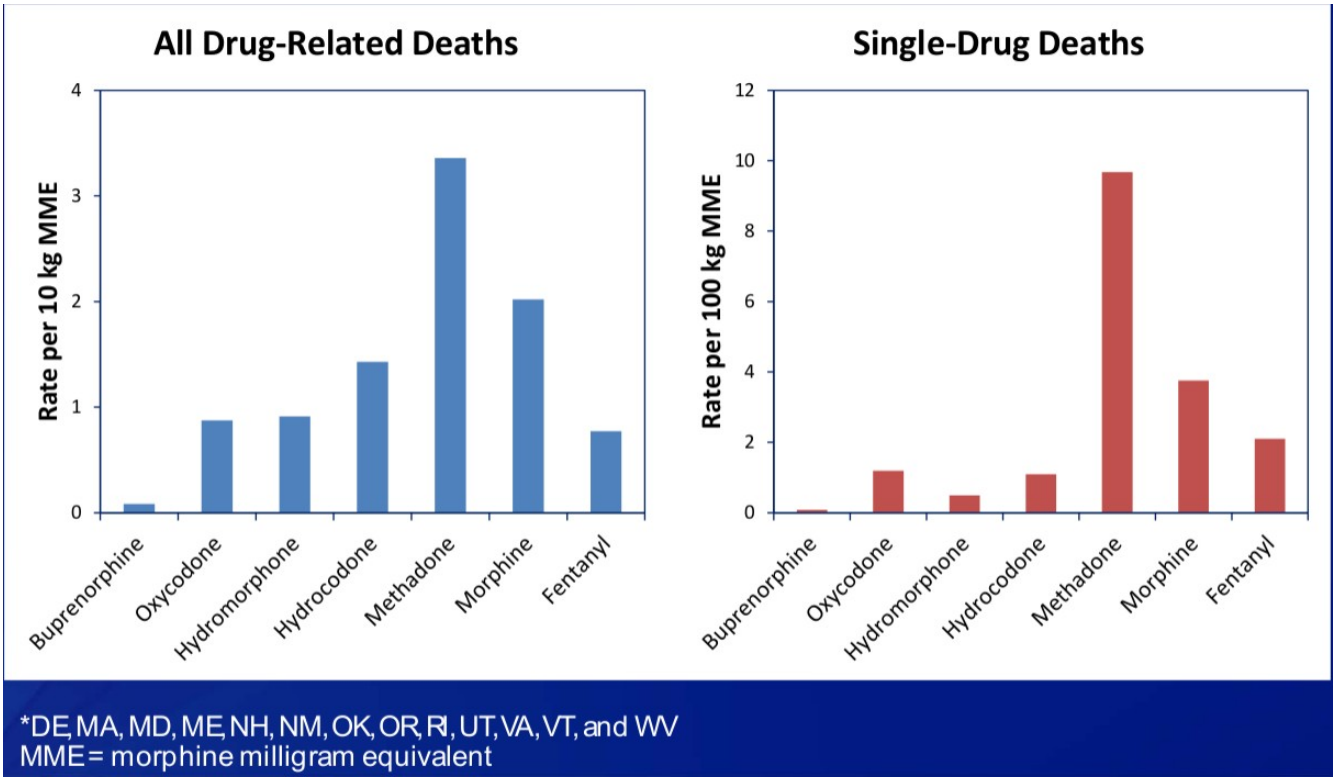


Illustration 8: Source: CDC 2012

The situation in the UK is equally dire. Importantly, the UK has documented what is also inferentially a circumstance that exists in BC. That is that methadone causes more deaths per user than heroin.

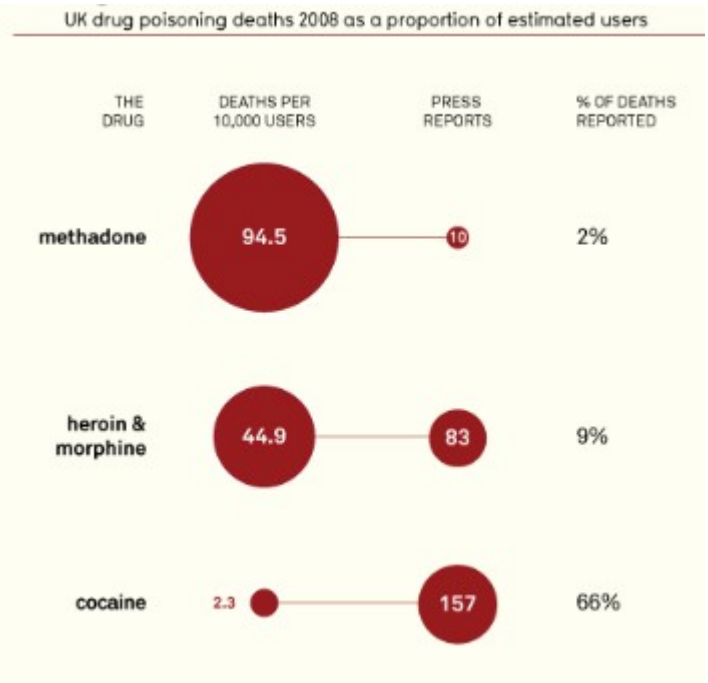
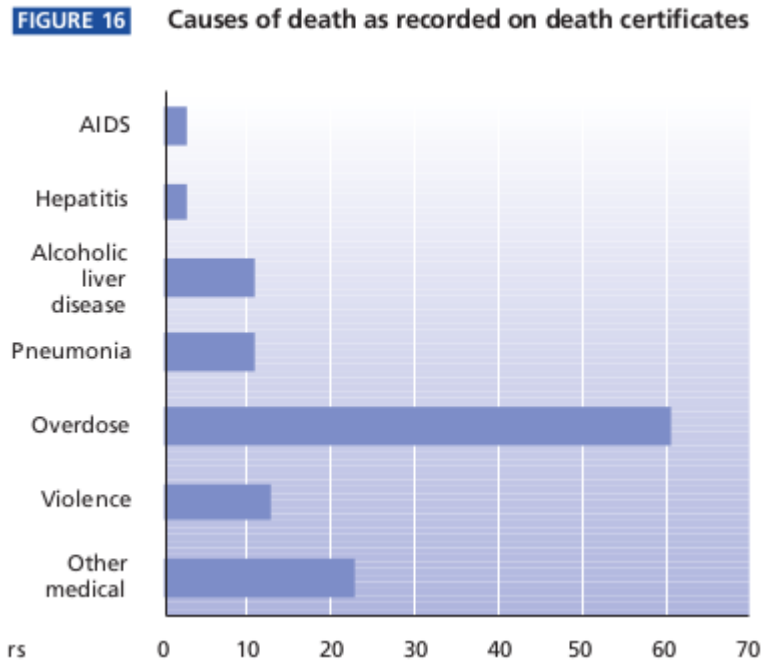


Illustration 9: Source: McCandless 2013

Sadly, the increased mortality for MMT has been the subject of academic interest since at least 2001. As seen below, overdose is by far the most likely cause of death of MMT clients. It's opioids which kill MMT patients and it's opioids that MMT gives them.

Illustration 10: Source: Gossop 2001)



Social Harms of Methadone

Just as the individuals in MMT carry significant risk, those outside the MMT program itself are also carrying risk.

There is a dearth of studies which explore the societal impacts of MMT. Nonetheless there are three areas which demonstrate the deleterious effect of MMT on the larger society. That situation mirrors the paucity of studies regarding the long term implications of MMT for individuals and the virtual absence of reported studies of BC's implementation of MMT. That MMT has a fifty year history in BC and no such studies exist brings to mind Conan Doyle's prescient observation that there is much to be learned when the dog doesn't bark.

One of the areas badly affected by MMT is the BC pharmacy industry.

> On Sept. 9, 2008, reports in Canadian print and television media revealed that certain pharmacies in Vancouver's Downtown Eastside were paying patients up to $10 a day to pick up methadone prescriptions at their pharmacy. (Nosyk 2009, Thomlinson 2008)

The effectiveness of this inducement to MMT clients may be understood when it is realized that $10 per day represents a 50% rise in monthly income for a social assistance recipient.

This author is in possession of a video recording of a pharmacist offering an inducement to the operator of a supportive recovery service. Payment was offered for each client that was placed on methadone and for whom delivery of the methadone would be made. The inducement offered in that case was $100 per client to initially place the client on methadone and a further $100 per month per client. Anecdotal evidence indicates that the current price for such 'service' has risen to $150 per month. Pharmacies making such offers include their 'own' doctors as part of the deal. Some would question the economics of such an offer. However, the inducement to the supportive recovery operator represents a two/thirds savings on the part of the pharmacy from the bribes being paid to the individual clients. The operators of supportive recovery facilities in BC place themselves at a distinct economic disadvantage, possibly amounting to several thousand dollars per month, when compared to operators who are accepting those inducements. The root cause of these inducements is the over-compensation of pharmacies for the services they render. This excess profit is being used to finance the 'inducements'.

The reputational cost to the pharmacy industry of such practices is incalculable.

The National Highway Traffic Safety Adminstration (NHTSA) has made the following findings in respect of the impact of methadone on the ability of the user to drive.

> Effects on Driving: The drug manufacturer cautions that methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, and that the sedative effects of the drug may be enhanced by concurrent use of other CNS depressants, including alcohol. In healthy, non-methadone using volunteers, single doses of methadone will impair driving ability. Numerous European studies of long- term methadone maintenance patients have shown that appropriately administered methadone does not cause significant psychomotor or cognitive impairment when administered regularly and when the subject abstains from all other drugs. However, in the majority of cases, patients did not exhibit stable abstinence from drug use and had an increased occurrence of simultaneous psychiatric/neurotic disorders or personality disturbances which, by themselves, could be a reason to doubt their driving ability. In Germany, the Joint Advisory Council for Traffic Medicine at the Federal Ministry of Transport, Building and Housing and the Federal Ministry for Health issued the following recommendation: Heroin addicts treated with methadone are generally not fit to drive; however, these patients may be considered fit to drive if they show a period of methadone substitution for more than a year; stable psychosocial integration; no evidence of the consumption of additional psychotropic substances; evidence of a subject’s readiness to feel responsible for himself/herself; therapy compliance; and no evidence of serious personality defects.
> DEC Category: Narcotic Analgesic.
> DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size

> constricted; little to no reaction to light; pulse rate down; blood pressure down; body temperature down. Other characteristic indicators may include muscle tone flaccidity, droopy eyelids, drowsiness, depressed reflexes, and dry mouth.
> Panel's Assessment of Driving Risks: Moderate to severely impairing in naïve or non-tolerant individuals, causing dose-dependent reductions in reaction time, visual acuity and information processing. Significant psychomotor impairment is not expected in tolerant individuals. Driving ability and driving fitness are nevertheless often limited because of consumption of additional psychotropic substances and psychopathological findings. (NHTSA 2013)

As the reader will now be aware, virtually none of the 14,000 BC MMT clients meet the requirements set out by German authorities as being necessary to warrant allowing a methadone user to drive. How many are actually driving or otherwise endangering society is yet another lacunae of BC MMT data.

One of the groups most likely to be advised to enter MMT are pregnant heroin-dependant women.

> Methadone maintenance treatment is considered the standard of care for women who are pregnant and dependent on opioids. (Health Canada Best Practices 2002)

The reasons for this advice have been succinctly set out:

> Methadone is a synthetic opioid, which provides a longer lasting "high" than most opioids, and is much less likely to be misused.
> It is usually prescribed as a substitute for heroin, and is associated with a more stable maternal lifestyle and less likelihood of stunted fetal growth or preterm birth. (Phys.org 2010)

Both the CPBC and CPSBC adhere to this advice. In neither case, however, do they or Health Canada discuss the impact on the child or the frequency, intensity or duration of Neonatal Abstinence Syndrome (NAS) suffered by the baby after methadone use. The interested reader will wish to discuss the impact of NAS on methadone babies to understand the horrific impact endured by 80% of babies born to methadone using mothers. This, yet again, is an area sadly lacking academic and research attention. No studies of the long term impact on children of BC's MMT mothers seem to have been published. Anecdotal reports by parents of fostered methadone babies reveal extended NAS of up to a year with continuing behavioural issues which are reportedly similar to those of Fetal Alcohol Syndrome.

Two studies have reported specific negative impacts of maternal methadone use.

> But most babies born to mothers, who are prescribed it during their pregnancy, have significant withdrawal symptoms, known as neonatal abstinence syndrome or NAS. These symptoms are severe enough to warrant treatment in up to 80% of cases.
> They assessed the eyesight of 20 children with vision problems, whose mothers had taken methadone during the pregnancy.
> Most of the children had also been exposed to either benzodiazepines (55%) or heroin (40%) while in the womb.
> Virtually all the children (95%) had poor eyesight in addition to which seven out of 10 had

> involuntary eye movement (nystagmus), while in half vision had not yet developed fully (delayed visual maturation).
> Eleven out of 12 children who had been treated for NAS had nystagmus, compared with only three out of eight whose NAS had not been severe enough to warrant treatment.
> One in three (35%) also had a squint (strabismus), while a similar proportion (30%) had blurred vision or long or short sightedness problems (refractive errors). And one in four had impaired brain function relating to sight.
> One in four children also had significant developmental problems, including developmental delay and cerebral palsy. (Phys.org, 2010)
>
> Impaired eye-tracking skills in 4-year-old children exposed to methadone or buprenorphine and tobacco prenatally may inhibit the development of some cognitive functions later in life. (Melinder 2013)

Given the possible life long impact on the neurological development of the children of MMT mothers, the absence of research is particularly offensive.

Methadone poses yet another danger for children.

> We identified 9,179 children exposed to a prescription opioid. The median age was 2.0 years (range newborn to 5.5 years), and 54% were boys. Nearly all exposures involved ingestion (99%) and occurred in the home (92%). Exposures to any opioid were associated with 8 deaths, 43 major effects, and 214 moderate effects. ... Nearly all exposures were to medications prescribed for adults in the household. The number of prescriptions filled for an opioid in an area correlated well with exposures in young children in the same area; children have access to household members' prescription drugs. (Bailey 2008)

Unfortunately, again, no BC agency appears to be tracking and reporting on this issue.

The reliance by medical and pharmaceutical personnel on a pharmacological treatment such as MMT is having a particularly acute impact within the Fraser Health Authority. Although refusing to document its policy, the Fraser Health Authority will not provide funding to any substance abuse treatment facility or organization that will not deliver the MMT.

As the following illustration makes clear, only 10% of persons presenting for substance abuse primarily use opioids. MMT is only for opioid users. No pharmocological treatments exist for other drugs. Thus Fraser Health is requiring that 100% of available Health funded response is shaped by a treatment that can only be provided for 10% of the clients.

Table 3: Primary problem substance use profiles for the BC Health Authorities (%).

	VCH[1]	FHA[2]	NHA	VIHA[3] (youth)	IHA	PHSA[4]
Alcohol	39.8%	32.1%	48.3%	32.3%		41.8%
Cannabis	15.2%	11.8%	15.9%	54.6%		23.0%
Cocaine/Crack	26.2%	34.7%	11.6%	6.5%		23.3%
Methamphetamines	3.1%	5.4%	1.2%	2.6%		0.5%
Rave/Club Drugs	2.5%	1.0%	0.0%	0.4%		1.1%
Sedatives	4.6%	0.0%	0.0%	0.0%		0.5%
Hallucinogens	0.2%	1.1%	0.1%	1.4%		0.0%
Opioids	6.1%	10.1%	5.7%	0.5%		3.3%
Inhalents	0.2%	0.0%	0.0%	0.3%		0.0%
Other	2.2%	3.8%	17.2%	1.4%		6.6%

Notes:

[1] Information is from The Crossing, jointly funded by VCH & FHA, Richmond HSDA & North Shore HSDA

[2] Data derived from reports provided by FHA.

[3] VIHA data only represents youth treatment services. Adult treatment data was unavailable.

[4] Data derived from stats provided by PHSA agencies

Illustration 11: Source:Chow 2010

Since less than 20% of persons presenting for substance abuse treatment are seeking the outcomes claimed by MMT (Mckeganey,2004), Fraser Health is diligently promoting the interests of, at most, 2% of substance abuse clients to the detriment of the remaining 98%.

The failure to address the needs of 98% of the population at risk has an extended negative impact on the rest of society. It is precisely those individuals which constitute the majority of the homeless.

> However, the published literature and key informants in BC confirm that addiction is the most prevalent mental health problem in both the street homeless and at-risk populations, followed by concurrent disorders and, less frequently, mental illness alone. ...
> If we focus on the absolutely homeless, non-housing service costs amount to about $644.3 million per year across the province. In other words, the average street homeless adult with SAMI in BC costs the public system in excess of $55,000 per year. Provision of adequate housing and supports is estimated to reduce this cost to $37,000 per year. This results in an overall 'cost avoidance' of about $211 million per year. (Patterson 2008)

The actual costs to society are even greater than discussed by Patterson. The costs of policing and crime that are driven by drug addiction were not included.

An Alternate Solution – The Abstinence Model

As noted above, individuals that present wanting help for their addictions are overwhelmingly seeking to cease their drug taking behaviour and become abstinent.

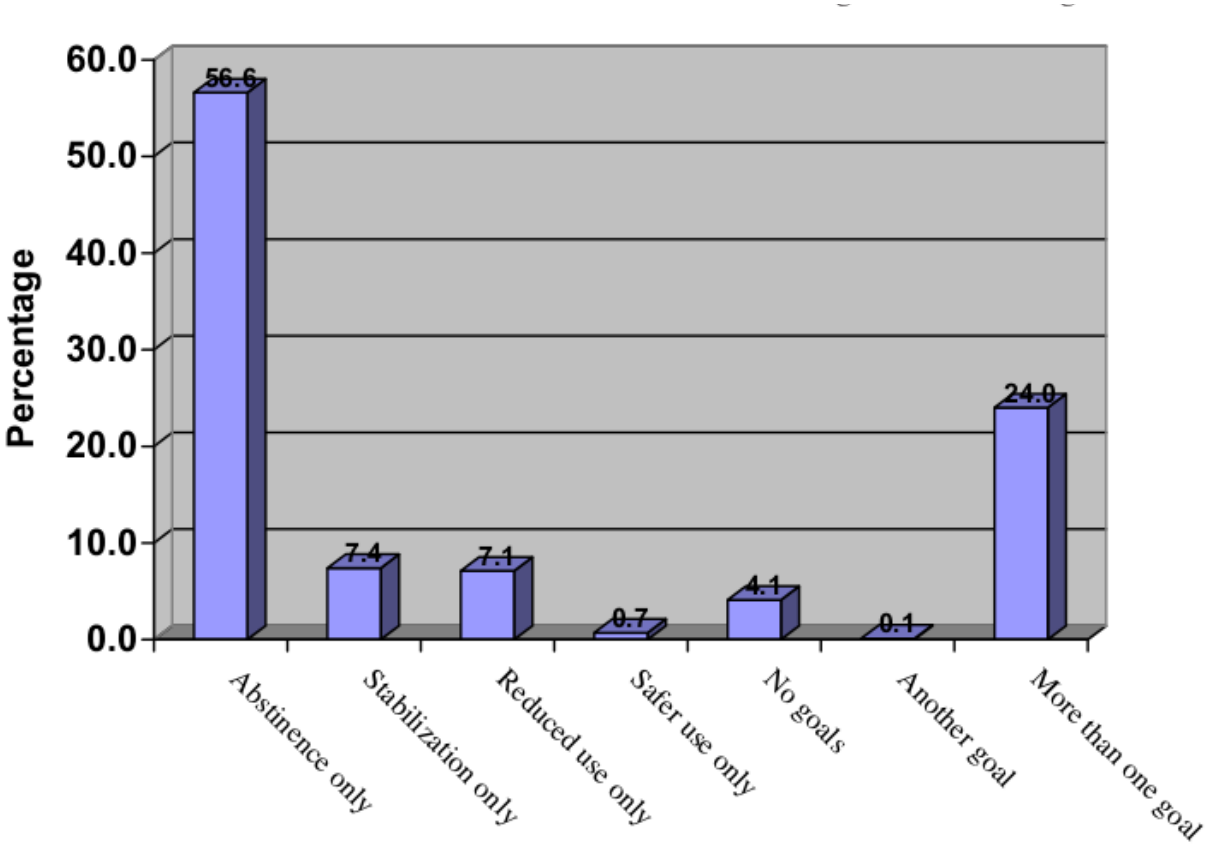


Figure 1. Treatment goals.

Illustration 12: Source: Mckegney 2004)

Despite the position adopted by Fraser Health Authority, the Provincial Health Officer has no apparent difficulty in supporting abstinent programs.

> I would like to assure readers there is no provincial policy against funding abstinence-oriented programs. Abstinence is, in fact, the ultimate goal of all substance use treatment. (Kendall 2013b)

Not only does Dr. Kendall endorse abstinence, he also recognizes the importance of meeting the stated needs of the clients. Fraser Health does neither.

> The science is really very clear: Both harm reduction and abstinence-based interventions are effective, but for different individuals at different points in their addiction cycle. ...

> However, given the high rates of concurrent mental health and other medical conditions that persons with addictions often face, to build a system without their contribution and expertise would be both simplistic and reprehensible. (Kendall 2013a)

In support of Dr. Kendall's endorsement of abstinence, two studies can be quickly cited.

> Excess mortality occurred only among those misusing alcohol or drugs at 2 years; nonmisusers had expected death rates. Disease and violent deaths were excessive among alcoholics, but only violent deaths exceeded expectancy among drug addicts. Of the 108 deaths, 66 were excess deaths, attributable to substance misuse and the associated way of life. However, among the 254 who were not misusing on follow-up, 19 died rather than the 51 who would have died if their mortality had been that of the persistent misusers. (Barr, 1984)

> Commitment to absolute abstinence at end of treatment was related to a lower risk of returning to use and longer time between the first use and relapse. (Hall 1990)

A further canard that Fraser Health personnel have used to justify their policy is their contention that successful substance abuse treatment cannot be accomplished without the willing participation of the client. They are not in favour of 'coerced' treatment which, for example, might be mandated by the courts.

The studies which actually address this issue are consistent. A comprehensive literature review found that:

> The preponderance of the research literature confirmed efficacy and cost benefits from coerced addiction treatment or providing addiction treatment in lieu of alternative consequences. Providing alternative consequences appeared to motivate patients/clients to comply with addiction treatment. The lack of research that showed coerced addiction treatment to be ineffective or adversive was striking. (Miller 2000)

A more recent Canadian study echoes those findings.

> A logistic regression analysis indicated that legal coercion was associated with greater readiness to change after controlling for addiction severity, prior treatment history, and gender. (Gregoire 2004)

An even more recent study found that:

> ...court-mandated clients reported significant and sustained reductions in illicit drug use and offending behaviours, and improvements in other areas of social functioning. (McSweeney 2007)

In British Columbia, the evaluation report of the Prolific Offender Management Model identified one abstinence-based program was effective with 74% of its clients remaining 100% abstinent and 100% crime free during their tenure with that program. Notably, prolific offenders are those with at least 30 Criminal Code convictions. (Rezansof 2001)

Conclusion

The foregoing review of the evidence in support of MMT has revealed that, in BC, the most that can be evidenced is that MMT may provide a 20% reduction in crime for 47.7% of its clients while retaining only 41% of its clients in treatment for one year.

More generally, the 2009 Cochrane review concluded that MMT is only effective at retaining individuals in MMT the sole benefit of which is reducing illicit opioid use. They found no other outcome to be statistically significant. Conveniently, this finding has been ignored.

The amount of illicit opioid use necessary to be considered a successful reduction is only 20% in BC and the single relevant report shows that only 41% of MMT clients managed that feat. There are no studies which demonstrate any other results for BC's implementation of MMT.

Against these meagre benefits must be weighed the costs.

In British Columbia, we pay at least $67 million dollars to accomplish this minimal reduction in illicit opioid use. The direct costs are likely much higher as the reported figures do not include any ancillary services or drug screening tests.

In BC, methadone clients are shown to be 267% more likely to require hospitalization than heroin users. This finding confirms the likelihood that BC also has a higher death rate for methadone than for heroin. Higher death rates have been confirmed by studies in other jurisdictions.

The sole pharmacological benefit of methadone, preventing withdrawal symptoms from heroin, is replaced with more extended withdrawal symptoms from methadone. All of the deleterious side effects of heroin are shared by methadone.

Assessing the precise costs for the impacts of MMT on the individual clients, for highway users and for children and families has been made impossible by the failure of BC health agencies to track and/or report the relevant statistics. Evidence from other jurisdictions demonstrates that those impacts are negative ones.

MMT is a treatment option for, at most, 10% of persons seeking treatment. Abstinence-based treatment options are appropriate for 100% of substance abuse problems. When the wishes of those seeking treatment are taken into account, MMT becomes, at best, a 2% solution.

While the evidence regarding the actual outcomes of MMT is sufficiently egregious in and of itself, it is made more so by the ready availability of effective, abstinence-based programs which are less costly, provide more certain benefits and avoid more harms.

Occam's razor provides the most useful tool for understanding the absence of BC studies showing any effectiveness for MMT. The most simple explanation is this – MMT simply doesn't work.

Bibliography

Amatoa, Laura, Marina Davolia, Carlo A. Peruccia, Marica Ferria, Fabrizio Faggianob, Richard P. Mattick. *An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research* . Journal of Substance Abuse Treatment 28 (2005) 321 – 329

Andersen, Jannike M. , Christine Klykken, Jørg Mørland. *Long-term methadone treatment reduces phosphorylation of CaMKII in rat brain.* Journal of Pharmacy and Pharmacology, 2012; 64 (6)

Andresen, M. A., & Boyd, N. *A cost-benefit and cost-effectiveness analysis of Vancouver's supervised injection facility.* International Journal of Drug Policy (2009),

Angres, Daniel H. MD, Kathy Bettinardi–Angres, APRN, CADC. *The Disease of Addiction: Origins, Treatment, and Recovery.* Dis Mon 2008;54:696-721

Au , David B.Sc. *The Management Of Drug Expenditures At British Columbia Correctional Centres* , Simon Fraser University 2005

Auditor General of British Columbia. *2013 Information Piece Health Funding Explained* .

Bailey, J. Elise MSPH , Elizabeth Campagna, MS , Richard C. Dart, MD, PhD. *The Underrecognized Toll of Prescription Opioid Abuse on Young Children* . J. Annals of Emergency Medicine 2008.

Baker, D.D. and A.J. Jenkins. *A comparison of methadone, oxycodone, and hydromorphone related deaths in Northeast Ohio*. J. Anal. Toxicol.32:165–171 (2008).

Barnett, Paul G. Ph.D. Sally S. Hui, B.A . *The Cost-Effectiveness of Methadone Maintenance* . The Mount Sinai Journal Of Medicine Vol. 67 Nos. 5 & 6 October/November 200 0

Barr, Harriet L., Derry Antes, Donald J. Ottenberg, Alvin Rosen , *Mortality of Treated Alcoholics and Drug Addicts: The Benefits of Abstinence* . J of Studies of Alcohol and Drugs, Vol.4 Issue 5, September 1984.

BC Coroners Service . *Deaths Among Homeless Individuals 2007-2010* .

BC Coroners Service . *Deaths of Inmates of Correctional Facilities in British Columbia, 2004 – 2011*

BC Coroners Service . *Illicit Drug Overdose Deaths 2004-2011* .

BC Coroners Service . *MDMA (Ecstasy) Related Deaths 2006-2011* .

BC Coroners Service . *Motor Vehicle Incident Deaths 2002-2011*

Bell J, Shanahan M, Mutch C, et al. *A randomized trial of effectiveness and cost-effectiveness of*

observed versus un-observed administration of buprenorphine-naloxone for heroin dependence. Addiction 2007 Dec; 102 (12): 1899-907

Blocker, Jack S. Jr, PhD. *Did Prohibition Really Work? Alcohol Prohibition as a Public Health Innovation*. Am J Public Health. 2006 February; 96(2): 233–243.

Bockmühl, M. and Ehrhart, G. (1949), *Über eine neue Klasse von spasmolytisch und analgetisch wirkenden Verbindungen,* I. Justus Liebigs Ann. Chem., 561: 52–86.

British Columbia Vital Statistics Agency . *Selected Vital Statistics and Health Status Indicators* . 2012.

Canadian HIV/AIDS Legal Network . *Opioid Substitution Therapy in Prisons: Reviewing the Evidence.* 2008

Carter, Connie I., Donald Macpherson, *Getting to Tomorrow: A Report on Canadian Drug Policy*. Canadian Drug Policy Coalition. 2013

Center for Disease Control (CDC). Vital Signs: Risk for Overdose from Methadone Used for Pain Relief — United States, 1999–2010 . Morbidity and Mortality Weekly Report , July 6, 2012 / Vol. 61 / No. 26 at 493.

Center for Substance Abuse Treatment. Detoxification and Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2006.

Chow, Clifton MA, David C Marsh MD CCSAM . *Addiction Treatment In British Columbia For 2008-2009.* AOD Monitoring Project Treatment Report 2009 .

Chow, Clifton MA, John Carsley MD MSc FRCPC . *Addiction Treatment In British Columbia For Fiscal 2009/2010* . AOD Monitoring Project Treatment Report 2009/2010 .

College of Pharmacists of British Columbia, *Professional Practice Policy #66 Policy Guide Methadone Maintenance Treatment (2013)*

College of Pharmacists of British Columbia*, PHARMACY METHADONEMAINTENANCE GUIDE (Contents revised April 2007; title revised September 2006)*

College of Pharmacists of British Columbia, *IN F O R M A T IO N B U L L E T IN , Changes to methadone formula coming Feb. 1, 2014*

College of Physicians and Surgeons of British Columbia (CPSBC) . *Methadone Maintenance Handbook.* December 2009

College of Pysicians and Surgeons of Nova Scotia. *CPSNS Methadone Maintenance Treatment Handbook.* 2012

Corkery, John M., Fabrizio Schifano, A. Hamid Ghodse and Adenekan Oyefeso . *The effects of*

methadone and its role in fatalities . Hum Psychopharmacol Clin Exp 2004; 19: 565–576.

Dolan, Kate A., James Shearer, Margaret MacDonald, Richard P. Mattick, Wayne Hall, Alex D. Wodak . *A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system* . Drug and Alcohol Dependence 72 (2003) 59 Á/65

Dole, Vincent P. MD and Marie E. Nyswander, MD, *Heroin Addiction – A Metabolic Disease* Arch Intern Med–Vol 120, July 1967

Dow, Kimberly, Alice Ordean , Jodie Murphy-Oikonen , Jodie Pereira , Gideon Koren , Henry Roukema , Peter Selby , Ruth Turner . *Neonatal Abstinence Syndrome Clinical Practice Guidelines For Ontario* . J Popul Ther Clin Pharmacol Vol 19(3):e488-e506; November 23, 2012 .

Dunn, Kate M. PhD; Kathleen W. Saunders, JD; Carolyn M. Rutter, PhD; Caleb J. Banta-Green, MSW, MPH, PhD; Joseph O. Merrill, MD, MPH; Mark D. Sullivan, MD, PhD; Constance M. Weisner, DrPH, MSW; Michael J. Silverberg, PhD, MPH; Cynthia I. Campbell, PhD; Bruce M. Psaty, MD, PhD; and Michael Von Korff, ScD. *Opioid Prescriptions for Chronic Pain and Overdose A Cohort Study* . Ann Intern Med. 2010;152:85-92.

Fingerhut. Lois. *Increases in Poisoning and Methadone-Related Deaths: United States, 1999-2005* . Health E-Stat . 2008.

Francis,Pam Msc , Shaun Black, MSc, MBA , Sarah Johnson, Bsc , Tom Payette, MSW, RSW. Evaluation of Methadone Maintenance Treatment Services: First Voice . Capital Health Addiction Prevention and Treatment Services , Halifax, Nova Scotia. 2005.

Fraser Health Authority . *2012/13 – 2014/15 Service Plan* . June 2012

Freiberger , Marianne. *How to measure life* . Retrieved from plus.maths.org.

Garner, Dr. Sarah. *The economics of health (Calculating QALYS)* March 2010. Retrieved from plus.maths.org.

Gerlach, Ralf . *A Brief Overview on the Discovery of Methadone.* INDRO e.V.Münster 2004.

Gibson, Amy, Louisa Degenhardt . *Mortality related to naltrexone in the treatment of opioid dependence: A comparative analysis* . NDARC Technical Report No. 229

Gomes, Tara MHSc; Donald A. Redelmeier, MD; David N. Juurlink, MD, PhD; Irfan A. Dhalla, MD, Msc; Ximena Camacho , MMath; Muhammad M. Mamdani, PharmD, MA, MPH . *Opioid Dose and Risk of Road Trauma in Canada A Population-Based Study.* JAMA Intern Med. 2013;173(3):196-201

Goodwin , Andrew. *Measuring the harm from illegal drugs: the Drug Harm Index 2005* . Home Office Online Report 22/07

Gossop , Michael. *Drug misuse treatment and reductions in crime: findings from the National Treatment Outcome Research Study (NTORS)*. National Treatment Agency for Substance Misuse. 2005.

Gossop,Michael, John Marsden and Duncan Stewart . *NTORS After Five Years The National Treatment Outcome Research Study Changes in substance use, health and criminal behaviour during the five years after intake* . National Addiction Centre . 2001.

Governale, Laura, *Outpatient Prescription Opioid Utilization in the U.S., Years 2000 – 2009* , Food and Drug Administration. July, 2010

Government Accountability Office, *METHADONE-ASSOCIATED OVERDOSE DEATHS , Factors Contributing to Increased Deaths and Efforts . GAO-09-341* March 2009

Gray , Dr Andy. *Systematic review of the safety of buprenorphine, methadone and naltrexone* . Background Document Prepared For Third Meeting Of Technical Development Group (TDG) For The WHO "GUIDELINES For Psychosocially Assisted Pharmacotherapy Of Opioid Dependence" 17-21 September 2007

Gregoire TK, Burke AC . *The relationship of legal coercion to readiness to change among adults with alcohol and other drug problems.* Journal of Substance Abuse Treatment [2004, 26(1):337-343]

Hall SM, Havassy BE, Wasserman DA. *Commitment to abstinence and acute stress in relapse to alcohol, opiates, and nicotine.* J Consult Clin Psychol. 1990 Apr;58(2):175-81.

Hart, W. Anton, Chair . Report of the Methadone Maintenance Treatment Practices Task Force Ontario Ministry of Health and Long-Term Care. 2007.

Health Canada. *Dispensing Methadone For The Treatment Of Opioid Dependence Guidelines For Pharmacists* . 1994

Health Canada. *Best Practices Methadone Maintenance Treatment* . 2002

Henningfield, Jack E., Neal L Benowitz, John Slade, Thomas P Houston, Ronald M Davis, and Scott D Deitchman. Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. Tobacco Control 1998;7:281–293

Inciardi J. A., Martin S.S., Butzin C.A. *Five-year outcomes of therapeutic community treatment of drug involved offenders after release from prison.* 2004 Crime and Delinquency, 50 (2), 88–107.

Institute of Health Economics. *The Cost Of Mental Health And Substance Abuse Services In Canada* . June 2010

Ivsins, A., Chow, C., Marsh, D., Macdonald, S., Stockwell, T. & Vallance, K. (2010). *Drug use trends in Victoria and Vancouver, and changes in injection drug use after the closure of Victoria's fixed site needle exchange.* (CARBC Statistical Bulletin). Victoria, British Columbia: University of Victoria.

Johnson, Sara L. *Impact of institutional methadone maintenance treatment on release outcome.* Research Branch, Correctional Service of Canada. 2001.

Joseph,Herman Ph.D. Sharon Stancliff, M.D. and John Langrod, Ph.D. *Methadone Maintenance Treatment (MMT): A Review of Historical and Clinical Issues* . The Mount Sinai Journal Of Medicine Vol. 67 Nos. 5 & 6 October/November 2000

Humeniuk, Rachel, Robert Ali, Jason White, Wayne Hall and Michael Farrell. *Proceedings Of Expert Workshop On The Induction And Stabilisaton Of Patients Onto Methadone* . Findings of an expert workshop. January 28th and 29th 1999 . Adelaide, South Australia

Kalivas, Peter W. Ph.D. *Predisposition to Addiction: Pharmacokinetics, Pharmacodynamics, and Brain Circuitry* . Am J Psychiatry 160:1, January 2003

Kendall,P.R.W. , OBC, MBBS, MSc, FRCP. *Decreasing HIV Infections Among People Who Use Drugs By Injection In British Columbia: Potential explanations and recommendations for further action* .Provincial Health Officer March 2011

Kendall, Perry. Letter to the Editor, The Province, March 16, 2013.

Kendall, Dr. Perry. Harm reduction one route of many . Maple Ridge Times. April 2, 2013

Kim, Theresa W. , Daniel P. Alford, Alan Malabanan, Michael F. Holick, Jeffrey H. Samet, *Low bone density in patients receiving methadone maintenance treatment.* Drug and Alcohol Dependence 85 (2006) 258–262.

Kimber, Jo, Lorraine Copeland, Matthew Hickman, John Macleod, James McKenzie, Daniela De Angelis, James Roy Robertson. *Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment.* BMJ, published online ahead of print 1 July 2010

Klatt, E. C., Mills, N. Z., and Noguchi, T. T., *Causes of Death in Hospitalized Intravenous Drug Abusers.* Journal of Forensic Sciences, JFSCA, Vol. 35, No. 5, Sept. 1990, pp. 1143-1148.

Kozlowski LT, Wilkinson DA, Skinner W, Kent C, Franklin T, Pope M. *Comparing tobacco cigarette dependence with other drug dependencies. Greater or equal 'difficulty quitting' and 'urges to use,' but less 'pleasure' from cigarettes.* JAMA. 1989 Feb 10;261(6):898-901.

Kraft MK, Rothbard AB, Hadley TR, et al. *Are supplementary services provided during methadone maintenance really cost-effective?* Am J Psychiatry 1997; 154: 1195–97.

Leavitt, Stewart B. PhD, Methadone-Drug* Interactions (*Medications, illicit drugs, & other substances) 3rd Edition . November 2005 . Addictions Treatment Forum.

Leikin, Jerrold B. MD . *Substance-Related Disorders in Adults* . DM, June 2007

Lipton,Douglas S. Ph.D . The Effectiveness of Treatment for Drug Abusers Under Criminal Justice Supervision . National Institute of Justice . 1995.

MacNeil Joan, Bernadette Pauly *Impact: a case study examining the closure of a large urban fixed site*

needle exchange in Canada . Harm Reduction Journal 2010, 7:11

Marie , Victoria. *Spirituality: its starring role in recovery from addiction* . Spirituality And Health International 8: 148–156 (2007)

Mallinckrodt Canada ULC . *Product Monograph Methadose*. 2013

Marsh, David C MD CCSAM, Annette Cooper BSc (hon), Clifton Chow MA . *Utilizing Treatment Data In B.C. Drug Surviellance 2007-2008* . AOD Monitoring Project Treatment Report 2007

Martens, L., Stockwell, T., Buxton, J.A., Duff, C., Macdonald, S., Richard, K., Chow, C., Ivsins, A., Michelow, W., Puri, A., Tu, A., & Zhao J. (2008). *Regional Variations and Trends in Substance Use and Related Harms in BC*. (CARBC statistical bulletin #4). Victoria, British Columbia: University of Victoria.

Mattick RP, Breen C, Kimber J, Davoli M , *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Review)* . 2009 The Cochrane Collaboration.

McCandless, David. *Deadlist Drugs.* InformationIsBeautiful.com

McFadden , Michael. *The Australian Federal Police Drug Harm Index: A New Methodology for Quantifying Success in Combating Drug Use* . Australian Journal of Public Administration 65(4):68-81 December 2006

McHugh, R. Kathryn, Bridget A. Hearon, and Michael W. Otto . *Cognitive-Behavioral Therapy for Substance Use Disorders* . Psychiatr Clin North Am. 2010 September ; 33(3): 511–525.

McLellan, A. Thomas , James R. McKay, Robert Forman, John Cacciola, & Jack Kemp. *Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring* . Addiction, 100, 447–458 . 2005.

Mckeganey , Neil. *The Lure And The Loss Of Harm Reduction In Uk Drug Policy And Practice* . Addiction Research and Theory December 2006; 14(6): 557–588

Mckeganey, Neil, Zoe Morris, Joanne Neale, Michele Robertson . *What Are Drug Users Looking For When They Contact Drug Services: abstinence or harm reduction?* Drugs: education, prevention and policy, Vol. 11, No. 5, 423–435, October, 2004

McSweeney, Tim, Alex Stevens, Neil Hunt and Paul J. Turnbull. *Twisting arms or a helping hand? Assessing the impact of 'coerced' and comparable 'voluntary' drug treatment options.* British Journal of Criminology, 2007, 47(3)

Melinder, Annika, Carolien Konijnenberg, Monica Sarfi . *Deviant Smooth Pursuit in Preschool Children Prenatally Exposed to Methadone or Buprenorphine and Tobacco affects Integrative Visuo -Motoric Capabilities. Addiction.* 06/2013

Miller, Dusty Ed.D. *Addictions And Trauma Recovery:*

An Integrated Approach . Psychiatric Quarterly, Vol. 73, No. 2, Summer 2002 (C 2002)

Miller, Norman S. M.D., Joseph A. Flaherty, M.D. *Effectiveness of coerced addiction treatment (alternative consequences) A review of the clinical research* . Journal of Substance Abuse Treatment 18 (2000) 9–16 .

Miller, Norman S., Fred G. Ninonuevo, Debra L. Klamen, Norman G. Hoffmann & David E. Smith. *Integration of Treatment and Posttreatment Variables in Predicting Results of Abstinence-Based Outpatient Treatment After One Year* . Journal of Psychoactive Drugs Volume 29, Issue 3, 1997

Ministry of Attorney General, Justice Services Branch ,Ministry of Public Safety and Solicitor General, Corrections Branch . *Downtown Community Court In Vancouver Interim Evaluation Report.* August 30, 2010

Ministry of Health Report . *Improving Health Services For Individuals With Severe Addiction And Mental Illness.* November 15, 2013

Ministry of Health Services, *Response from the B.C. Government RE: Methadone Maintenance Treatment in British Columbia, 1996-2008: Analysis and Recommendations* . September 2010

Ministry of Health Services, Ministry of Children and Family Development. *Healthy Minds, Healthy People: A Ten-Year Plan to Address Mental Health and Substance Use in British Columbia.* November 1, 2010.

Ministry of Health Services, Ministry of Children and Family Development. *Healthy Minds, Healthy People: A Ten-Year Plan to Address Mental Health and Substance Use in British Columbia: Monitoring Progress: 2012 Annual Report* . 2013

Modesto-Lowe V, Brooks D, Petry N. *Methadone deaths: risk factors in pain and addicted populations*. J Gen Intern Med. 2010;25(4):305–9.

National Highway Traffic Safety Administration (NHTSA). *Drugs and Human Performance FACT SHEETS -Methadone.* Retrieved from http://www.nhtsa.gov/people/injury/research/job185drugs/methadone.htm. 2013.

National Institute on Drug Abuse . *Principles Of Drug Addiction Treatment A Research-Based Guide Third Edition* . National Institutes of Health , U.S. Department of Health and Human Services . 2012

National Institute on Drug Abuse . *Principles Of Drug Addiction Treatment Criminal Justice Populations A Research-Based Guide* . National Institutes of Health , U.S. Department of Health and Human Services . 2012

National Treatment Agency for Substance Misuse , *Estimating the crime reduction benefits of drug treatment and recovery* . 2012

National Treatment Strategy Working Group. (2008). *A Systems Approach to Substance*

Use in Canada: Recommendations for a National Treatment Strategy. Ottawa: National Framework for Action to Reduce the Harms Associated with Alcohol and Other Drugs and Substances in Canada .

Nosyk, Bohdan MA, Aslam H. Anis PhD . *Commentary: Medical profiteering: the economics of methadone dispensation* . CMAJ • MAY 26, 2009 • 180(11)

Nosyk, Bohdan PhD, Daphne P. Guh MSc, Nicholas J. Bansback PhD, Eugenia Oviedo-Joekes PhD, Suzanne Brissette MD, David C. Marsh MD, Evan Meikleham MSc, Martin T. Schechter MD PhD, Aslam H. Anis PhD. *Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment* . CMAJ 2012.

Ontario Tobacco Research Unit. *Quitting Smoking in Ontario.* 2013.

Oviedo-Joekes,Eugenia Ph.D., Suzanne Brissette, M.D., David C. Marsh, M.D., Pierre Lauzon, M.D., Daphne Guh, M.Sc., Aslam Anis, Ph.D., and Martin T. Schechter, M.D., Ph.D. *Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction* . N Engl J Med 361;8 . 2009

Parkes, Tessa. *British Columbia Methadone Maintenance Program A Qualitative Systems Review*. 2010

Parkes, Dr Tessa & Bill Nelles . *Methadone maintenance treatment (MMT) in British Columbia, Canada: Lessons for health care system change and research practice* . Centre for Addictions Research of BC. 2011.

Patterson Michelle, Julian M Somers , Karen Mcintosh , Alan Shiell , Charles James Frankish . *Housing and Support for Adults with Severe Addictions and/or Mental Illness in British Columbia* . Centre for Applied Research in Mental Health and Addiction, Faculty of Health Sciences, Simon Fraser University. 2008

Paulus I, Halliday R. *Rehabilitation and the narcotic addict : results of a comparative methadone withdrawal program.* Can Med Assoc J. 1967 Mar 18;96(11):655- 9.

Peirce, Jessica M. PhD; Nancy M. Petry, PhD; Maxine L. Stitzer, PhD; Jack Blaine, MD; Scott Kellogg, PhD; Frank Satterfield; Marion Schwartz, MSW; Joe Krasnansky, CSW; Eileen Pencer, MSW; Lolita Silva-Vazquez, MA; Kimberly C. Kirby, PhD; Charlotte Royer-Malvestuto, MEd; John M. Roll, PhD; Allan Cohen, MA, MFT; Marc L. Copersino, PhD; Ken Kolodner, ScD; Rui Li, MS. *Effects of Lower-Cost Incentives on Stimulant Abstinence in Methadone Maintenance Treatment A National Drug Abuse Treatment Clinical Trials Network Study* . ARCH GEN PSYCHIATRY/ VOL 63, FEB 2006

Phys.org. *British heroin substitute may be associated with wide-ranging sight problems.* Apr 21, 2010

Pirie, T., Jesseman, R., Di Gioacchino, L., & National Treatment Indicators Working Group. *National Treatment Indicators Report: 2011–2012 Data.* Canadian Centre on Substance Abuse. 2014.

Provincial Health Officer (PHO). *BC Methadone Maintenance System Performance Measures*

2011/2012 . 2013.

Rehm, J., D. Baliunas, S. Brochu, B. Fischer, W. Gnam, J. Patra, S. Popova, A. Sarnocinska-Hart, B. Taylor, E. Adlaf, M. Recel, E. Single . *The Costs Of Substance Abuse In Canada 2002 Highlights* . Canadian Centre on Substance Abuse (CCSA) March 2006

Reist , Dan. *Methadone Maintenance Treatment in British Columbia, 1996-2008 Analysis and Recommendations* . Centre for Addictions Research of BC, University of Victoria . 2010

Rezansof, Stefanie, Akm Moniruzzaman, Julian M. Somers. *An Initiative to Improve Outcomes Among Prolific and Priority Offenders in Six British Columbia Communities: Preliminary Analysis of Recidivism.* Simon Fraser University. 2011.

Rich , Marcia L. *Integrating Shamanic Methodology into the Spirituality of Addictions Recovery Work* . Int J Ment Health Addiction (2012) 10:330–353 .

Rieckmann,Traci Ph.D.; Anne E. Kovas, M.P.H. & Beth A. Rutkowski, M.P.H. *Adoption of Medications in Substance Abuse Treatment: Priorities and Strategies of Single State Authorities* . Journal of Psychoactive Drugs SARC Supplement 6, September 2010.

Sharma, Anjali, Peter L. Flom, Jeremy Weedon and Robert S. Klein. *Prospective study of bone mineral density changes in aging men with or at risk for HIV infection.* AIDS 2010,24:000–000

Silverman, Kenneth; Robles, Elias; Mudric, Timothy; Bigelow, George E.; Stitzer, Maxine L. *A Randomized Trial of Long-Term Reinforcement of Cocaine Abstinence in Methadone-Maintained Patients Who Inject Drugs*. Journal of Consulting and Clinical Psychology, Vol 72(5), Oct 2004, 839-854

Simpson DD, Joe GW, Broome KM, Hiller ML, Knight K, Rowan-Szal GA. *Program diversity and treatment retention rates in the Drug Abuse Treatment Outcome Study (DATOS).* Psychol Addictive Behav 1997; 11(4): 279–293.

Single,Eric, David Collins, Brian Easton, Henrick Harwood, Helen Lapsley, Pierre Kopp and Ernesto Wilson. *International Guidelines for Estimating the Costs of Substance Abuse Summary of 2001 Edition* Canadian Centre on Substance Abuse (CCSA) 2001

Smith, Frances M., Lisa A. Marshall. *B arriers to effective drug addiction treatment for women involved in street-level prostitution: a qualitative investigation* . Criminal Behaviour and Mental Health 17: 163–170 (2007)

Smyth B, Fan J, Hser YI. *Life expectancy and productivity loss among narcotics addicts thirty-three years after index treatment.* J Addict Dis. 2006;25(4):37–47.

Somers , Dr. Julian, Dr. Ernest Drucker , Dr. Jim Frankish , Dr. Brian Rush. *Housing for People with Substance Use and Concurrent Disorders: Summary of Literature and Annotated Bibliography* . The Centre for Applied Research in Mental Health and Addiction , Faculty of Health Sciences , Simon Fraser University . January 2007

Statistics Canada. *Alcohol and illicit drug dependence* . Supplement to Health Reports, Volume 15, 2004 . Catalogue No. 82-003

Statistics Canada. *Health Profile.* January 2013.

Stockwell, T., Vallance, K., Martin, G., Macdonald, S., Ivsins, A., Chow, C., Greer, A., Zhao, J., Duff, C., Lucas, P., Marsh, D., Michelow, W. & Treno, A. (2010) *The price of getting high, stoned and drunk in BC: A comparison of minimum prices for alcohol and other psychoactive substances.* CARBC Statistical Bulletin #7, Victoria, British Columbia: University of Victoria.

Strang, John, Janie Sheridan, Claire Hunt, Bethanne Kerr, Clare Gerada and Michael Pringle . *The prescribing of methadone and other opioids to addicts: national survey of GPs in England and Wales* . British Journal of General Practice 2005; 55: 444–451

Strassels SA. *Economic burden of prescription opioid misuse and abuse.* J Manag Care Pharm 2009; 15:556–562

Strike, Carol J. , William Gnama, Karen Urbanoski, Benedikt Fischera, David C. Marsh, Margaret Millson. *Factors predicting 2-year retention in methadone maintenance treatment for opioid dependence* . Addictive Behaviors 30 (2005) 1025–1028

Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Substance Abuse Treatment. *National Treatment Improvement Evaluation Study (NTIES)*. Substance Abuse and Mental Health Services Administration: Rockville, MD, 1992–1997.

Substance Abuse and Mental Health Services Administration. *Detoxification and Substance Abuse Treatment* . 2006.

Substance Abuse and Mental Health Services Administration. *Emerging Issues in the Use of Methadone* . Substance Abuse Treatment Advisory, Spring 2009 Volume 8 Issue 1

Substance Abuse and Mental Health Services Administration . *Medication-Assisted Treatment for Opioid Addiction* . U.S. Department Of Health And Human Service. 2009

Substance Abuse and Mental Health Services Administration. *Methadone-Related Emergency Department Visits Involving Nonmedical Use* . The DAWN Report. January 19, 2012

Substance Abuse and Mental Health Services Administration. *Methadone Mortality: A 2010 Reassessment* . July 2010

Sutton, Stephen . B*ack to the drawing board? A review of applications of the transtheoretical model to substance use* . Addiction (2001) 96, 175– 186

Taylor, Avril, Jennifer Champion, Alex Fleming. *The Role of Methadone Maintenance in Scottish Prisons: Prisoners' Perspectives* . Institute for Applied Social and Health Research, University of Paisley .

Tomlinson K. *Pharmacy paid addict kickback: hidden camera.* CBCnews.ca; 2008. Available: www.cbc.ca/canada/british-columbia/story/2008/09/07/bc-prescription -for-profit.html?ref=rss&loomia_si=t0:a16:g2:r1:c0.135526

TOSCA. *Report of the Toronto and Ottawa Supervised Consumption Assessment Study, 2012*

Unattributed. *How many people are receiving Methadone Hydrochloride mixture for opiate dependence in Scotland and what are the prescribing costs per person?* ISD Scotland . 2005

Unattributed. *What treatments are effective for people who abuse methamphetamine?* National Institute on Drug Abuse. 2014

Urban Health Research Initiative. Drug Situation in Vancouver Report. British Columbia Centre for Excellence in HIV/AIDS . June 2013

Vallance, Kate, Evelyn Souza. *Estimated Age and Sex Standardized Rates of Illicit Drug Caused Hospitalizations per 100,000 People for BC and Health Authorities by ICD-10 Codes, 2002-2009.* Spreadsheet. CARBC 2011

Vallance, K., Martin, G., Stockwell, T., Macdonald, S., Chow, C., Ivsins, A., Buxton, J., Tu, A., Sandhu, J., Chu, T. and Fair, B. (2012). *Overdose Events in British Columbia: Trends in Substances Involved, Contexts and Responses*. CARBC Statistical Bulletin #8, Victoria, British Columbia: University of Victoria.

Warner, Margaret Ph.D.; Li Hui Chen, Ph.D.; Diane M. Makuc, Dr.P.H., Robert N. Anderson, Ph.D.; and Arialdi M. Miniño, M.P.H. *Drug Poisoning Deaths in the United States, 1980–2008* . NCHS Data Brief No. 81 December 2011

Webster, Lynn R. MD *Methadone-related deaths.* Journal of Opioid Management 1:4 September/October 2005

Whelan, Paul J, Kimberly Remski . Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds . Journal of Neurosciences in Rural Practice. 2012 .

White, Ian R., Dan R Altmann, Kiran Nanchahal . *Alcohol consumption and mortality: modelling risks for men and women at different ages* . BMJ VOLUME 325 27 JULY 2002 .

Zaric, Gregory S, Andrew W Brennan, Michael Varenbut, Jeff M Daiter. *The cost of providing methadone maintenance treatment in Ontario, Canada* . Am J Drug Alcohol Abuse , 2012

Zarkina,Gary A., Laura J. Dunlapa, Katherine A. Hicksa and Daniel Mamob . *Benefits and costs of methadone treatment: results from a lifetime simulation model.* Health Econ. 14: 1133–1150 (2005)

Zhao, Jinhui, Gina Martin, Scott Macdonald and Tim Stockwell . *The Prevalence of Alcohol and illicit drug Use in British Columbia* . Unpublished. Available at

http://carbc.ca/Portals/0/AOD/GeneralPopulationSurveys/CADUMSReport0809.pdf 2011