

The Comparison of Prescriptions Dispensed For Methadone Maintenance
Patients to Non-Methadone Maintenance Patients for the Treatment of Chronic
Diseases using PharmaNet Data

by

Anna Maruyama
B.Sc.Pharm, University of British Columbia, 1999

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

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Supervisory Committee

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Abstract

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Context: Modifiable risk factors in older methadone maintenance treatment (MMT) patients may put them at a greater risk of acquiring chronic diseases.

The paucity of literature regarding the well-being and service needs of older MMT patients required investigation to determine whether these patients are treated for and adhere to chronic disease medications(s) comparably to those not on MMT.

Objective: This study compared the proportion of MMT patients to a matched control group treated with first-line medications for four chronic diseases: hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus and depression. As a secondary outcome measure, this study also examined the adherence comparability between the two groups.

Method: This case control study used prescription claims data from the BC Ministry of Health's PharmaNet database from October 1, 2008 to December 31, 2009. Each MMT patient was individually matched with a control subject in terms of age, sex, social assistance coverage and local health area. Both groups consisted of 143 men and 56 women for a total of 400 participants. Persons 50 years of age and older, residents of BC, and had prescriptions filled during

October 1, 2008 to December 31, 2009, were randomly selected from the PharmaNet database.

Results: Odds ratios (ORs) were calculated to compare the odds of MMT patients to non-MMT patients on a first-line medication for each chronic disease under investigation. ORs were 0.865 for hypertension (ns), 0.738 for diabetes (ns) and 4.176 for depression ($p < 0.001$). For COPD the OR could not be calculated as no controls were treated for COPD; however, 11.6% of the MMT group were prescribed COPD medications which was significantly higher than the controls ($p < .001$). Adherence was calculated using continuous measures of medication availability (CMA) “by patient” and “by medication class” during patients’ persistent periods (continuous use periods) CMA(1), as well as the entire study period CMA(2). By patient, the mean CMA(1) showed no difference between the groups (non-MMT group: 91.9%, SD=15.8, CI=95% vs MMT group: 89.7%, SD=22.2, CI=95%). The mean CMA(2) was statistically different ($p < 0.05$) between the groups (non-MMT group: 70.5%, SD=25.3, CI=95% vs MMT group: 60.8%, SD=29.1, CI=95%). By medication class, CMA(1) was 80-100% for most medication classes for both groups except for insulins and inhalers in the MMT group which fell between 40-79%. The CMA(2) for most medication classes was 60-86% in the non-MMT group and 30-76% in the MMT group. However, the differences between the groups were not statistically significant.

Conclusion: Odds ratios for the treatment of all four chronic diseases differed. Therefore, looking at each chronic disease separately may be worthwhile to suggest potential targets for intervention. Disease-specific tailored interventions

related to lifestyle risk factors, comorbid medical conditions, and adherence to chronic medications could potentially improve the overall health of older MMT patients. However, development of appropriate interventions and treatments requires research that properly recognizes the physical and mental health problems faced by older MMT patients (Rosen, Hunsaker, Albert, Cornelius, & Reynolds III, 2010).

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Introduction

Individuals that are psychologically and/or physically dependent on synthetic and/or natural opioids (e.g.: codeine, morphine and heroin), can be prescribed methadone as part of a treatment program. Methadone is a long-acting, synthetic opioid prescribed to replace the misused opioid(s), in order to alleviate withdrawal symptoms, reduce cravings, and prevent relapse (Jamison, Kauffman, & Katz, 2000).

Much of the research on older adults related to addiction and its effects on health has concentrated on the misuse of alcohol and prescription medications (Rosen, Smith, & Reynolds, 2008). However, the effects of opioid dependence on the health of older adults has not been as widely studied (Rosen et al., 2008; Rosen et al., 2010). Previous research has examined the physical and mental health characteristics of older (> 50 years old) opioid dependent individuals on methadone maintenance treatment (MMT) and found that these individuals are generally in poorer physical and mental health than the general population (Fareed, Casarella, Amar, Vayalapalli, & Drexler, 2009; Hser et al., 2004; Loftwall, Brooner, Bigelow, Kindbom, & Strain, 2005; Rosen et al., 2008). Adding to this disadvantage, studies suggest that these individuals encounter barriers to accessing primary health care and social services compared to the general population (Fischer, Cruz, & Rehm, 2006; Loftwall et al., 2005; Popova, Rehm, & Fischer, 2005; Rosen et al., 2008; Rosen et al., 2010).

Due to their lifestyle, opioid dependent individuals are at an increased risk for adverse health problems such as infections, extensive co-morbidity and

premature mortality (Popova et al., 2005). Some of these opioid related health problems may be improved through MMT (Rosen et al., 2008). However, as this population ages, these problems may be compounded by age-related chronic diseases such as hypertension, chronic obstructive pulmonary disease (COPD), and diabetes. There are common risk factors to these diseases including tobacco use, poor diet, lack of physical activity, and alcohol use (Yach, Hawkes, Gould, & Hofman, 2004). These lifestyle related behaviours are commonly seen in older MMT patients (Elkader, Brands, Selby, & Sproule, 2009; Fareed et al., 2009; Hser et al., 2004; Nolan & Scagnelli, 2007; Rosen et al., 2008). This group of individuals have diverse and complex needs as a result of the combination of risks associated with drug use and age-related chronic diseases.

In British Columbia, a physician must be authorized by the College of Physicians and Surgeons of British Columbia and exempted under the *Controlled Drugs and Substances Act* in order to prescribe methadone for opioid dependence. This is separate from the authorization required to prescribe methadone for pain. Therefore, if a patient's family doctor is not authorized to prescribe methadone for maintenance, a patient may have a family doctor and a separate methadone doctor. The separation between the family doctor and the specialty methadone doctor presents a range of challenges in coordinating care. This distinct and separate care fails to take into consideration the unique challenges faced by MMT patients that may limit their access to treatment. Even when these patients have access to treatment, they are at risk for poor compliance with prescribed treatments (Druss & von Esenwein, 2006). The gap

between health needs and available services is greatest in medically vulnerable populations such as MMT patients (Druss & von Esenwein, 2006). As a result of this gap, opioid users tend to place high demands on hospital services, as they tend to seek help only when medical conditions have advanced and symptoms have become severe (Popova et al., 2005). This can be costly, and cause significant burden on services.

This research builds on previous studies conducted in the United States (US) on the health status of older MMT patients (Fareed et al., 2009; Hser et al., 2004; Loftwall et al., 2005; Rosen et al., 2008). This study's aim was to compare the health status of older MMT patients to non-MMT patients in British Columbia (BC), Canada by examining the prescriptions dispensed to both populations and their adherence to these dispensed medications. This was done by comparing the treatment(s) and adherence to these treatment(s) of the following chronic diseases: hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus (both Type I and Type II), and depression. Given the high mental illness comorbidity in opioid dependent populations (Loftwall et al., 2005), depression was included in the investigated disease treatments. Although depression is a non-fatal illness, if untreated, it can cause disease burden as there can be significant disability during disease presentation. Also, depression alone or together with another chronic disease, can be significantly associated with poorer health than having no chronic disease or having one other chronic disease (Moussavi, Chatterji, Verdes, Tandon, & Patel, 2007). These chronic diseases were chosen for a number of reasons. All have the potential to cause significant

disease burden, limiting activities of daily living and loss of economic output as ongoing care is required (Anderson & Horvath, 2004). They can all contribute to premature mortality. They also share common risk factors that are likely elevated in the older MMT population which would be detected with even a modest sample size. Recommended pharmacotherapy of these diseases has been established and publicized in BC, and therefore, treatments between MMT and non-MMT patients could be compared by mining the provincial prescription database (PharmaNet). Finally, prevalence rates of these 4 diseases have been examined in older US MMT patients and the general population. This allowed for investigation of any disparity between expected prevalence and treatment of these diseases in BC.

Background

Methadone Maintenance Treatment

In 2003, it was estimated that there were more than 80,000 illicit opioid users in Canada (Popova et al., 2005). In recent years, research has suggested that illicit opioid use is not only limited to heroin but rather increasingly includes legally available and illegally diverted prescription opioids (Fischer et al., 2006). There has been a dramatic increase in opioid prescribing in Canada over the past 10 years that may have led to an increase in opioid misuse (Ontario Ministry of Health and Long Term Care, 2007). Illicit opioid use is associated with considerable harm, risks, and health and social problems relating specifically to the individual's drug use. Those who are dependent on opioids may be dependent on either oral or injectable forms of opioids. Although MMT does not cure opioid dependence, it is a medical treatment that can help manage the addiction. It is a component of harm reduction which aims to reduce or eliminate harmful consequences of the addiction (e.g.; needle sharing and criminal activity associated with addiction) to the individual, families, communities and society. As part of the MMT program, patients are required to consume daily oral doses of methadone dissolved in juice. When methadone is diluted in juice and consumed orally, it does not produce euphoric effects to the extent that other immediate release opioids do, and attenuates the euphoric effect of other self-administered opioids. Although there are a number of treatment options that can be considered, in Canada, the best studied and most common treatment for opioid dependence has been largely limited to MMT (Fischer et al., 2006).

Hypertension and Treatment

Hypertension is the most treatable risk factor for cardiovascular disease (Wolf-Maier et al., 2003). Hypertension is defined as the presence of a persistent office blood pressure reading of 140mmHg or more for systolic blood pressure, or 90mmHg or more for diastolic blood pressure. The results from the Canadian Community Health Survey in 2010, reported that the prevalence of hypertension in the Canadian population between the ages of 55-64, was 32% for men and 29% for women. In BC, the prevalence rates were only slightly lower in the same demographic (28% for men and 27% for women) compared to the national rates (BC Ministry of Health, 2003). The results of the Canadian Heart Health survey indicated that there are still a considerable number of Canadians with untreated high blood pressure (59%) (Khan & Chockalingam, 2002). Out of those diagnosed with hypertension, 80% received prescription medications (Tran et al., 2007).

There are many factors that can increase the risk of hypertension: age (risk increases with age), race (more common among blacks), family history, gender (middle age for men, and over 60 for women), tobacco use, stress, weight, sedentary lifestyle, and drinking too much alcohol (having more than 2-3 drinks per sitting) (Government of British Columbia., 2009). Although some risk factors for hypertension (e.g.; family history) are not modifiable, others such as lifestyle related behaviours are. These behaviours may be more common amongst older MMT patients than in the general population. For example, the prevalence of cigarette smoking in MMT patients in the US ranges from 85-98%

(Elkader et al., 2009) compared to 23% in the US general population (Fareed et al., 2009). Several studies have reported worse physical functioning and bodily pain in older (>50 years) MMT patients than the general population within the same age group. This could potentially contribute to a more sedentary lifestyle (Hser et al., 2004; Loftwall et al., 2005; Rosen et al., 2008). Regular alcohol use may be lower in older MMT patients (17.6%-33.3%) (Hser et al., 2004; Rajaratnam, Sivesind, Todman, Roane, & Seewald, 2009; Rosen et al., 2008) than in the general population (51.6%) (Centre for Disease Control and Prevention, 2012a). However, alcohol use was self-reported in these studies and could have been under reported. As these behaviours may be more elevated in the older MMT population, it would be expected that there would be a higher prevalence of hypertension in the older MMT group than the non-MMT group.

Although the diagnosis and treatment of hypertension appears simple, this disease is poorly managed. Only 16% of Canadians that have been diagnosed with high blood pressure have adequately controlled it with medications (Government of British Columbia., 2009). The goal of treatment is to reduce blood pressure in order to reduce hypertension associated morbidity and mortality. This can be achieved by a combination of healthy lifestyles and pharmacological treatment. When using pharmacologic treatment, an effective, individualized treatment plan should balance the benefits along with the potential risks. The treatments outlined for the chronic diseases in this study are from the *Clinical Practice Guidelines and Protocols in British Columbia* (Government of British Columbia., 2009). For uncomplicated hypertension, mono-therapy with a

low-dose thiazide diuretic is considered as first-line treatment. For hypertension complicated with comorbid conditions, other classes of medications may be prescribed as first-line. Appendix 1 lists all the first-line medications in each class along with their available doses, and coverage status under BC's provincial Pharmacare program.

Chronic Obstructive Pulmonary Disease and Treatment

Chronic obstructive pulmonary disease (COPD) is an irreversible lung disease characterized by long-term or permanent inflammation and narrowing of the small airways connected to the lung. The progressive airway obstruction that characterizes COPD leads to symptoms of breathlessness, cough and sputum production. Those who have the disease also experience symptom exacerbations. As the disease advances, the end result is death. COPD patients also commonly present with several other comorbidities including cardiovascular disease, mental health disorders (e.g.; depression and anxiety), musculoskeletal disorders, and systemic complications that can also significantly reduce quality of life (The Canadian Lung Association, 2009).

According to a report commissioned by The Canadian Lung Association (2007), 4.6% of Canadians have COPD with an additional 4.9% of the population reporting having COPD symptoms without yet being diagnosed (The Canadian Lung Association, 2009). In 2003-2004, the number of people with COPD in British Columbia was approximately 4.3% of the population aged 45 and older (Platt, 2004). The main risk factor causing COPD is cigarette smoking (approximately 80-90% of cases). The other 10-20% of causes are: second hand

smoke, occupational exposure to dusts and chemicals, the rare genetic disorder alpha-1 antitrypsin deficiency, air pollution, and having repeated lung infections as a child (The Canadian Lung Association, 2009). Given the high prevalence of smoking in older MMT patients in other studies (Elkader et al., 2009; Fareed et al., 2009; Hser et al., 2004; Rosen et al., 2008), it would be expected that the prevalence of COPD would be higher in the older MMT group than the non-MMT group.

Doctors and public health officials agree that it is dramatically under-diagnosed and under-treated. The therapeutic goals that are part of managing COPD are to prevent disease progression, treat the symptoms of the disease, improve health status and reduce mortality. Although there is no cure for the disease, pharmacological treatment of COPD can improve symptoms, reduce the frequency of exacerbations and improve quality of life. Medications used as first-line therapy in COPD are bronchodilators that help to open up the airways, reduce air trapping and dyspnea. There are two classes of bronchodilators: short acting beta₂-agonist and anticholinergics. Appendix 2 lists the different medications in each class along with their available doses, dosage forms, and coverage status under BC's provincial Pharmacare program.

Diabetes Mellitus and Treatment

Diabetes mellitus is a metabolic disorder characterized by the presence of high blood glucose levels due to defective insulin secretion, defective insulin action or both (Canadian Diabetes Association, 2008). Over time, high blood glucose levels can cause complications, dysfunction and failure of various organs

(including the kidneys, eyes, nerves, heart and blood vessels), and premature death. There are two classifications of diabetes: type I and type II. In type I diabetes, the pancreas does not produce insulin where as in type II, the pancreas may not be producing enough insulin and/or the body is not properly able to utilize the insulin it makes. It is unknown exactly what causes type I diabetes although genetics may be involved. In 2005, 5.5% of the Canadian population had diabetes (Canadian Diabetes Association, 2008). This percentage has most likely grown given Canada's demographic trends with an aging population, immigration from high-risk populations (e.g.; Aboriginal, South Asian, Asian or African descent) and increase in the number of obese individuals (Canadian Diabetes Association, 2008). According to the Canadian Diabetes Association, 7.3% of the BC population had diabetes in 2010 which is expected to rise to 10.3% by 2020.

Risk factors contributing to type II diabetes are: being overweight, age (over 40), physical inactivity, high blood pressure or high cholesterol, family history of diabetes, belonging to high risk ethnic populations (e.g.: Aboriginal, African, Hispanic), a history of gestational diabetes, and having other vascular diseases (Government of Canada., 2012). Many of the risk factors for diabetes are not modifiable however, behaviours such as healthy eating (to maintain a healthy weight) and physical activity can be. Only one study reported the weight of their older MMT participants and found that 54.6% were overweight (Hser et al., 2004). This prevalence was similar to the 52.3% of people (both sexes) in BC between the ages of 45-64 that were overweight in 2007-2008 (ActNow BC,

2010). In general, opioid dependent individuals are typically underweight at the beginning of MMT (Mysels & Sullivan, 2010) and may gain weight on MMT however, there is nothing to suggest that the problem with obesity is greater than in the general population. Studies have had conflicting results regarding the prevalence of diabetes in older MMT patients compared to the general population (Fareed et al., 2009; Hser et al., 2004; Rosen et al., 2008). As the modifiable risk factors of obesity and physical inactivity may be similar between the MMT group and the non-MMT group, it would be expected that the prevalence of diabetes would be similar in these groups.

Insulin therapy remains the mainstay treatment for type I diabetes.

Appendix 3 lists the various types of available insulin and their coverage status under the Pharmacare program. The treatment of type II diabetes is more complicated as there is debate over which antihyperglycemic agent(s) should be used initially (including insulin) and which agents should be used subsequently. There are a variety of medications in the alpha-glucosidase inhibitor, biguanide, insulin, insulin secretagogue (sulfonylureas and nonsulfonylureas), and insulin sensitizer classes that can be used alone initially, or in combination with another medication to treat type II diabetes. Appendix 4 is a list of the recommended first-line treatments in the various medication classes, the available doses and coverage status under the Pharmacare program.

Depression and Treatment

A major depressive episode may be characterized by persistent (at least 2 weeks) sadness, often associated with somatic symptoms, such as difficulty

sleeping and decreased energy causing significant social/occupational dysfunction (Hahn, Reist, & Albers, 2006). These symptoms must be a change from usual functioning, and are not a result of medical conditions and/or medications/drugs. For many patients, depression can be considered a chronic disease because of the recurrent nature of the disease and the long-term treatments that are sometimes necessary. Depression is often missed in people with chronic illness, and is also associated with increased rates of death and disability from cardiovascular disease. The lifetime prevalence for depression for Canadians aged 46-64 was 12.4% (Pattern et al., 2006) which was similar to the prevalence found in BC in the same demographic (11.8%) (Goldner et al., 2002).

Individuals at high risk for a major depressive episode are those with a comorbidity, psychological/physical trauma, unexplained somatic complaints, chronic pain, other psychiatric disorders, and family history of mood disorder. The relationship of comorbidity for opioid dependence and depression is complex. In opioid dependent individuals, the question of whether depression is an independent disease, dependence is the cause of the disease, or the disease is the cause of the dependence is not very clear (Fischer et al., 2006; Nunes, Sullivan, & Levin, 2004). Regardless of the relationship, many studies have reported a high prevalence of depression in opioid dependent populations including older populations on methadone (Fischer et al., 2006; Loftwall et al., 2005; Nunes et al., 2004; Rosen et al., 2008). As well, mental health or emotional well-being was found to be lower in older MMT patients than in the general population in some studies (Hser et al., 2004; Loftwall et al., 2005;

Rosen et al., 2008). With this, it would be expected that the prevalence of depression would be higher in the MMT group than the non-MMT group.

Depression, is again a disease that is under-diagnosed as the World Health Organization (WHO) Psychological Problems in General Healthcare Study has found. The study findings revealed that only 42% of patients with depression were diagnosed appropriately by their primary care physicians. There are a variety of medications in four different medication classes that are used as first-line antidepressants. Appendix 5 lists the different medication classes: novel action, reversible monoamine oxidase inhibitor (RIMA), serotonin and norepinephrine reuptake inhibitor (SNRI) and selective serotonin reuptake inhibitor (SSRI), and the medications available in each class, the available doses, and their coverage under the Pharmacare program.

Adherence

Adherence is defined as “the extent to which a person’s behaviour coincides with medical or health advice” (Farmer, 1999; Hess, Raebel, Conner, & Malone, 2006). Adherence to a treatment plan is especially critical in chronic diseases where treatment is necessary for the reduction of long-term consequences. However, non-adherence to chronic medication(s) has been reported among patients in a variety of settings (Andrade, Kahler, Frech, & Chan, 2006). Substance dependent patients that also have a chronic disease and/or psychiatric illness are at a particularly high risk of poor adherence (Weiss, 2004). There are several distinct types of non-adherent behaviours that can occur: The patient may miss doses, the patient may stop the medication(s), and/or the

patient may take the medication(s) erratically. All of these behaviours can decrease drug efficacy, cause adverse effects and lead to suboptimal outcomes. The effectiveness of treatments for diseases such as hypertension and diabetes are very dependent on adherence to a treatment regimen. However, fewer than 40% of patients with hypertension, 50% of patients with COPD and depression, 60% of patients with Type I diabetes, and 85% of patients with Type II diabetes take their medications as prescribed (Cramer, 2004; Rand, 2005; Weiss, 2004). The assessment of medication adherence is important in understanding the factors related to poor adherence, identifying patients for intervention, and evaluating clinical and economic outcomes related to poor adherence.

Review of the Literature

The databases PubMed, Medline, and PsycINFO were used to search for relevant articles. As methadone maintenance treatment has only been available since the sixties, (Fareed et al., 2009) studies published in English between 1960 to the present were considered. Rosen et al (2011) conducted a systematic review examining the physical and mental health characteristics of adults 50 years of age and older that attended methadone maintenance treatment programs in the United States. Although the review of the literature showed that opiate dependent patients suffer from a variety of comorbid medical conditions (Health Canada, 2008) there were only a total of four studies that compared the physical and mental health status of older methadone maintenance patients with the general population.

In Hser et al (2004), a prospective cohort study (1964-1998) was conducted

using interviews and medical testing in order to examine the health conditions of 108 male surviving opioid dependent criminal offenders. At the time of medical examination, the mean age of the participants was 58.4. Results showed that 58.3% had high blood pressure. 6.4% of those with high blood pressure were taking medications to treat blood pressure. The rate of known hypertension was only slightly higher than for US males aged 55-64 (50.7%) in this study.

Approximately 13.3% of the participants were considered potentially diabetic as reflected by high blood glucose levels, with 5.3% reporting use of insulin or oral antihyperglycemics. The prevalence of elevated glucose in the study population was much higher than for US males aged 45-64 (5.9%). The majority of the participants (84.7%) smoked cigarettes at the time the study was conducted with one-third showing abnormal lung function and a diagnosis of lung disease. This was 2.4 times higher than the rate observed in the general US male population. Overall, the participants showed high rates of morbidity compared to the general male population in the same age category. At the time the study was conducted, most of the participants were not on methadone maintenance, however, they were admitted to a compulsory drug treatment program at the California Civil Addict Program from 1962 to 1964.

In Rosen et al (2008), face-to-face interviews were conducted to an outpatient clinic sample of 140 methadone maintenance patients over the age of 50 in order to assess their physical and mental health status as compared to population norms within the same age bracket. There were 92 men, and 48 women and participants had a mean age of 53.9 years (SD=4.01). Participants

were asked about a variety of chronic conditions in addition to taking the SF-12v2 survey (surveyee's view about their health) to measure a range of physical health issues. With regards to physical health, 44.9% of the participants had hypertension, 22.1% had chronic lung disease, 11.4% had diabetes and 87.1% reported smoking at the time the study was conducted. As well, 57.7% of respondents reported having fair to poor physical health. The analysis of mental health disorders showed that depression was the most common with 32.9% of all the participants having had a major depressive disorder. Nearly half of the participants (47.1%) reported taking psychotropic medications for a mental health problem. The results found that the physical and health conditions among the methadone maintenance patients were typical of those who were much older than in the general population.

In Fareed et al (2009), records from 91 patients over 40 years of age who were either currently or had previously been maintained on methadone maintenance treatment at the Atlanta VA Medical Centre during 2002-2007 were evaluated. Information on demographics, addiction severity index (ASI) scores (i.e.; semi-structured interviews to detect problems in seven areas: medical status, employment/support, drug use, alcohol use, legal status, family/social status and psychiatric status), diagnosis of several chronic diseases (e.g.; diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, cancer and hepatitis B and C), and tobacco use were collected. The patients' physical history was confirmed either by lab tests or clinicians' notes. Patients were categorized into three groups based on their current methadone

treatment status: retained in treatment, dropped out, or deceased. The study population was primarily African American men, with a mean age of 56, hepatitis C positive and intravenous drug users. Approximately 62% of participants had hypertension, 43% had diabetes, 23% had COPD and over 85% of the participants were smokers. Even though the participants in the retained treatment group had the lowest percentage of diabetes (18%) amongst the other treatment groups, this was still higher compared to 9.6% of the general population (over 20) who had diabetes at the time the study was conducted. The results found that the study participants had a much higher prevalence of medical illnesses and risk factors than the general population.

In Loftwall et al (2005), the health status of 41 older and 26 younger opioid maintenance patients were compared to age and sex-matched U.S. population norms. The older patients were over the age of 50 and the younger patients were between the ages of 25-34. The mean age for the older participants was 53.9 years (SD=0.6) and 20 of the older participants were female. Opioid maintenance patients received either methadone or L-alpha-acetylmethadol (similar to methadone but longer acting) at the Addiction Treatment Services outpatient program at the Johns Hopkins Bayview Medical Center. Medical problems and current prescription medication use was self-reported (i.e.; they completed a medical questionnaire). Older participants reported significantly higher rates of cardiovascular problems than the younger participants (53.7% vs. 15.4%, $p<0.001$), with hypertension as the most common cardiovascular problem reported in the older participants (51.2% vs. 3.8% $p<0.001$). There was no single

predominant cardiovascular disease in the younger participants. COPD was present in only 1 case (2.4%) in the older group, and diabetes was not reported. Depression was the most common diagnosis in both groups. The study reported 43.9% of older participants were taking 3 or more daily medications, compared to 3.8% of younger participants. There was no mention as to what medications the participants were taking. Both age groups had poorer health-related quality of life scores compared to age and sex-matched normative samples.

The studies reviewed were conducted in the United States and published between 2000 and 2008. The participants in the studies were all over the age of 50, and the health status of study participants were compared to the US general population of the same age category. Only two studies compared prevalences of the chronic diseases found in their study population with US population norms within the same age group. In Hser et al (2004), the prevalence of both hypertension and diabetes in their study population was higher than in the US male population within the same group, and Fareed et al (2009) reported that the prevalence of diabetes in their retained study group was also higher than in the general population. With the exception of Fareed et al (2009), where the patients' physical history was confirmed either by lab tests or clinicians' notes, the other studies used interviews and medical questionnaires to collect and measure self-reported medical problems. In Hser et al, the participants underwent a medical examination and blood pressure was measured using a digital sphygmomanometer. Three of the studies mentioned participants taking medication for medical condition(s). Two studies mentioned what types of

medications participants were taking and in Hser et al, 5.4% of hypertensive patients were taking anti-hypertensives but their blood pressures were not controlled. Medication adherence was not mentioned in any of the studies. Table 1 shows a summary of the reviewed studies. Table 2 is a depiction of the prevalence found in the four chronic diseases adapted from the Centre of Disease Control and Prevention in the US population (Centre for Disease Control and Prevention, 2011a; Centre for Disease Control and Prevention, 2011b; Centre for Disease Control and Prevention, 2012b; Centre for Disease Control and Prevention, 2012c) within the same age group as the reviewed literature's study population. Compared to the general US population older MMT participants in most of the reviewed studies had higher prevalence of hypertension, COPD and depression. In Loftwall et al (2005), although the prevalence of COPD in the older MMT participants was only 2.4% the n was very small (n=41). The three studies that reported diabetes prevalence in their study population had either similar, lower or higher prevalence's than the US population.

Table 1: Summary of the Physical/Mental Health Status of Older Methadone Maintenance Patients

Study	Setting	Sample Size	Mean Age	Percentage of MMT Patients with Chronic Diseases	Percentage of Patients taking Medications
Hser et al. (2004)	Los Angeles, USA: California Civil Addict Program	108	58.4	58.3% Hypertensive 13.3% Diabetic 34.6% Abnormal Lung Function	6.4% for Hypertension 5.3% for Diabetes
Rosen et al. (2008)	Midwestern City, USA: Free-standing methadone clinic	140	53.9	44.9% Hypertensive 22.1% Chronic Lung Disease 11.4% Diabetic 32.9% Major Depressive Disorder	47.1% Psychotropic
Fareed et al. (2009)	Atlanta, USA: Atlanta Veterans Affairs Centre	91	55.7	62.3% Hypertensive 43.0% Diabetic 23.0% COPD	Not mentioned
Loftwall et al. (2005)	Baltimore, USA: Johns Hopkins Medical Centre	41	53.9	51.2% Hypertensive 2.4% COPD 34.1% Major Depressive Disorder	43.9% taking 3 or more daily medications

Table 2: Prevalence of Study Chronic Diseases in US Population

Chronic Disease	Age Group	Prevalence		Year Data Was Collected
Hypertension	45-54	Men 33.6%	Women 33.0%	2005-2008
	55-64	Men 51.3%	Women 52.7%	
COPD	45-54	Men 3.9%	Women 7.5%	2007-2009
	55-64	Men 6.4%	Women 8.7%	
Diabetes	45-64	12.3%		2010
Depression	40-59	Men 7.0%	Women 12.0%	2007-2010

Note: Adapted from Centre for Disease Control and Prevention. (2011a). 2005-2008. *High blood pressure-Levels Vary by Age*. Retrieved 03/27, 2012, from <http://www.cdc.gov/bloodpressure/facts.htm>; Centre for Disease Control and Prevention. (2011b). 2007-2009. *Prevalence of COPD among adults aged 18 and over, by age group and sex: United States, annual average*. Retrieved 03/27, 2012, from <http://www.cdc.gov/nchs/data/databriefs/db63.htm> ; Centre for Disease Control and Prevention. (2012b). 2010. *Diabetes-Percentage of Civilian, Non-institutionalized Population with Diagnosed Diabetes, by Age, United States*. Retrieved 03/27, 2012, from <http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm> Centre for Disease Control and Prevention. (2012c). 2007-2010. *Depression-Prevalence of Current Depression Among Persons Aged >12 years, by Age Group and Sex United States, National Health and Nutrition Examination Survey*. Retrieved 03/27, 2012, from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6051a7.htm>

PharmaNet

Prescription claims data can provide unobtrusive information regarding a patient's fill/refill history and can provide information on gaps in therapy.

Although this method does not assess medication consumption, medication fill/refill behaviour can be assessed. A requirement that must be met to use prescription claims in order to assess medication adherence is that all prescription records for each patient must be included. BC's PharmaNet is a system that supports a more patient-centered approach to medication

management, as medication profiles can be shared between healthcare members through the use of this technology. In 2007, 47 million prescription claims were processed through PharmaNet and the system flagged more than 24 million potential drug interactions (Government of British Columbia., 2008). With a network that provides real-time information sharing, PharmaNet can help identify and prevent over-consumption of prescription medications intentionally or unintentionally, prescription fraud, drug interactions, dosage errors, allergic reactions, and patient compliance issues. PharmaNet supports drug dispensing, drug monitoring and claims processing by assisting the pharmacist with a total of seven individual checks on a prescription. As well, it can promote cost-effective use of medications, offer authorized health professionals comprehensive medication information they need to provide quality care, and provide immediate claims adjudication under the BC PharmaCare program (Government of British Columbia., 2008).

Those who have access to PharmaNet are the patients themselves (they can request a printed copy of their personal data stored on PharmaNet), pharmacists (access is granted only when fulfilling their professional duties while dispensing a prescription), the College of Pharmacists of British Columbia in order to regulate the profession and manage PharmaNet medication data, physicians such as emergency physicians and dispensing physicians in order to view medication histories, the College of Physicians and Surgeons of British Columbia in order to monitor prescribing patterns of their members, other healthcare providers such as non-pharmaceutical suppliers like prosthetic or

ostomy suppliers for the purpose of adjudicating claims (they do not have access to medication histories), and finally the Ministry of Health for payment data (they also do not have access to medication histories). It is a mandatory process in which all prescription medications dispensed by community pharmacies in B.C. are recorded on the system. As there is no choice to opt out of using PharmaNet, it may be perceived that it is easy to obtain patient records. Confidentiality is a common concern for information stored electronically, however, all PharmaNet users must sign a confidentiality agreement before being granted access and must provide a unique ID (usually a license number or initials) each time when logging onto PharmaNet leaving an electronic footprint every time a patient's profile is accessed (Government of British Columbia., 2008). This allows auditing by the governing bodies. In addition, patients can limit access to their information by asking their pharmacist to attach a keyword to access their PharmaNet profile. This keyword would be required before the patient's profile could be accessed. However, in cases of emergency the keyword can be over-ridden.

PharmaNet records a variety of information such as the patient's name, address, telephone number, gender, and date of birth, all medications dispensed within the past 14 months, any reported allergies as well as who reported the allergy (patient, pharmacist, physician), current or chronic medical conditions as well as who reported these conditions, whether the patient is restricted to a specific physician and/or specific pharmacy, and claim information including eligibility and coverage of medications. PharmaNet also stores a current list of

all British Columbia licensed doctors, dentists, pharmacists, veterinarians, optometrists, podiatrists, mid-wives and nurse practitioners with prescribing authority including license numbers, office address and phone numbers. Any restrictions these practitioners may have with regards to prescribing is also available. A list of all available medications, their benefit status and their respective drug information are also stored.

As we move forward towards building a provincial electronic health record, PharmaNet will play an important role within this circle. PharmaNet is in the process of being upgraded and will be renamed PharmaNet e-Rx (Government of British Columbia., 2007). Currently, medications given to patients as samples, trial courses and over the counter medications are not recorded on PharmaNet. As well, medication profiles only include medications dispensed in community or outpatient pharmacies. PharmaNet e-Rx will include samples, trial courses, over the counter medications, hospital stay information (including discharge and HIV medications), as well as medications dispensed by the BC Cancer Agency. Prescriptions will be retained on the system for 60 months compared to the current 14 months (Government of British Columbia., 2007). The current system does not formally track prescription pick-up although all pharmacies are required to reverse prescriptions not picked up within a month. PharmaNet e-Rx will require the pharmacy to record that a patient has collected their prescription(s) and confirm whether they have actually taken the medication(s). There are certain medications that Pharmacare does not cover or only partially covers. This can be a problem especially for patients on social assistance as they may

not be able to afford the entire cost of the medication. Normally medications that are on the Pharmacare formulary would be entirely free to these patients. In order for these medications to be covered, physicians can apply for a special authority for these patients if the patient meets criteria as set out by Pharmacare. The existing system requires that doctors either phone in the request or fax in the forms. PharmaNet e-Rx will automate processing for routine special authority requests, as physicians will be able to submit them electronically for immediate adjudication. Healthcare providers will be able to determine if a special authority exists for a patient, and if so when it expires. These improvements should help shorten waiting periods for special authority approval so that patients can begin therapy sooner. E-prescribing will also be a part of the new system upgrades. This will cut down on the time lost clarifying prescriptions and errors made from illegible handwriting. In order to get this into place, computer systems will have to replace the largely paper based health records in doctors' offices so that prescriptions can be transmitted directly to PharmaNet e-Rx. PharmaNet e-Rx will check the prescription against the patient's medication profile and immediately send out drug use evaluation information such as drug interactions back to the prescriber. After the prescriber reviews and confirms these messages, it will be added to PharmaNet e-Rx where the pharmacist will then be able to retrieve the electronic prescription. The future upgrades will be integrated into BC's electronic health records that will give health professionals a more complete patient profile required for clinical decision-making that will help to improve patient safety, and efficient care. Although PharmaNet is already

routinely used to support health policy, decision-making and research for clinical practice, the upgrades will provide a more complete database.

Although there are many different adherence measurement techniques (e.g.: pill counts, self-reports, medication event monitoring systems (MEMS), serum or urine drug level monitoring, prescriptions claims data), all have their limitations and no single measure can be considered the gold standard for all types of adherence research. Although the value and limitations of prescription claims data in estimating medication adherence for both health care services and population-based research have been previously recognized, several studies have used prescription claims data to determine the rate or degree of adherence with prescribed therapies (Farmer, 1999; Grymonpre, Cheang, Metge, & Sitar, 2006; Steiner & Prochazka, 1997).

Three provincial studies were found that compared either BC's PharmaNet system or Manitoba's Drug Program's Information Network (DPIN) with other adherence techniques for adherence research. In Dahri et al (2008), the accuracy of PharmaNet was assessed for adherence assessment in patients with heart failure taking beta-blockers. A six-month prospective, longitudinal assessment was conducted comparing adherence measures from PharmaNet data versus the MEMS device. As a secondary outcome, the study also compared adherence from PharmaNet and the Morisky score (the score from a self-reported medication-taking behaviour questionnaire). Patients were recruited from the outpatient heart function clinic and pre-transplant clinic at St. Paul's hospital in Vancouver. The participants' average age was 61 ± 10 , with

86% being male. Patients were required to use the MEMS device over a continuous time period that included at least 2 beta-blocker prescription refills entered on PharmaNet. Adherence was calculated as the days supply divided by the actual days to refill multiplied by 100. Out of 43 patients included in the analysis, the adherence from PharmaNet was $97.8\% \pm 11.8\%$ and MEMS was $97.1\% \pm 7.3\%$. The limit of agreement between PharmaNet and MEMS adherence was $6.8\% \pm 18.5\%$. Although this correlated to a high level of agreement between the two methods, when the confidence interval was taken into consideration (-11.7 to 25.3) the limit of agreement was only moderate. The Morisky score and PharmaNet adherence generally agreed for most patients. The study found that PharmaNet tended to underestimate adherence for patients with lower adherence rates, while overestimating for those with higher rates compared with MEMS. The findings suggested that PharmaNet data accurately reflected medication adherence for most patients.

In Grymonpre et al (2006), prescription claims data using Manitoba's DPIN system was used to estimate refill adherence compared to pill counts for all prescribed medications where at least one of the prescribed medications was an ACE inhibitor (ACEI) for blood pressure. The 151 participants were 65 years and older (mean age was 77), non-institutionalized, taking 2 or more prescribed medications (including an ACEI), and recruited from community pharmacies. Three home interviews were conducted over 4 months and DPIN data was collected for 10 months on each participant. Adherence from DPIN was measured by continuous medication availability (CMA) and continuous multiple-

interval measure of medication gaps (CMG) “by patient” and “by drug” based on the methodologies used by Steiner et al (1997). CMA was calculated as the sum of the days supply divided by the total days from the first dispensation date to the last dispensation date (Steiner & Prochazka, 1997). CMG was calculated as the total number of days in treatment gaps divided by the first dispensation date to the last dispensation date (Steiner & Prochazka, 1997). Medications were included in the analysis only if there were at least 3 or more dispensations from the DPIN data. At least 3 pill counts were conducted during the home interviews. McNemar’s test was used to determine the strength of the agreement (in percent) between DPIN and pill count. The by drug comparison included drugs identified from both DPIN and pill counts so that a paired comparison could be made. Adherence was calculated from 3786 prescription fills for 714 drugs and 142 participants. Adherence rates calculated from DPIN and pill counts were very high by patient and by drug. The study suggested that the low concordance between CMA and/or CMG and pill count by patient were due to the validity of using DPIN for non-discrete dosage forms or medications prescribed for as needed use. The concordance by drug for overall medications for CMA and pill count was much higher (79% and 88% for ACEIs specifically) than by patient for CMA and pill count. CMG and pill count was 85% for overall medications and 95% for ACEIs. The study concluded that the high concordance between DPIN and pill counts by drug suggested that the refill medication rate is consistent with the rate at which medications are consumed.

In George and Shalansky (2006), prescription claims from PharmaNet were compared with self-reported adherence in order to identify characteristics associated with medication non-adherence for patients with heart failure. Participants were recruited from a heart failure clinic or pre-heart transplant clinic at St. Paul's Hospital in Vancouver, BC. Overall, there were 350 participants, 69.4% of which were males. The mean age of the participants was 61.7 ± 14.4 . A minimum of 3 months of medication consumption was required to determine adherence from PharmaNet. Adherence from PharmaNet was calculated using CMA where the number of days supply was divided by the actual no of days to refill. Self-reported adherence questionnaires included Beliefs About Medicines questionnaire, Health Belief Model scale, and the Morisky scale. Smokers, two or fewer medication administration times, and a positive response to having to change a daily routine to accommodate taking the heart failure medication were independent predictors of refill non-adherence. Refill non-adherence was found in 22.3% of participants compared to 38.3% reported by self-report. The study found a moderate concordance between PharmaNet refill adherence and self reported adherence. All three studies used CMA calculations to measure adherence and supported the validity of the provincial claims databases as there was a moderate to high concordance between the prescription claims data and the other method of adherence used in each study.

Objectives

Many of the studies found that both the physical and mental health status of older methadone or opiate addicted patients were typical of individuals much older, or worse than the general population in the same demographic (Loftwall et al., 2005; Hser et al., 2004; Rosen et al., 2008). In addition, risk factors and lifestyle related behaviours that may be elevated in the older MMT population led to expectations that the MMT group would have higher prevalence of hypertension, COPD, and depression, and similar prevalence of diabetes to the non-MMT group. However, this population may have poorer access to care as well as being stigmatized for being on MMT that could possibly contribute to inferior care and poorer treatment outcomes (Parkes & Reist, 2010). Also, many opiate treatment programs and mental health services in BC are isolated from mainstream medical clinics, potentially making access to chronic disease treatment more difficult. These competing expectations made it necessary to formulate a competing hypothesis. It was hypothesized that the MMT group would have higher or lower treatment in all four of the chronic diseases than the non-MMT group. Focusing on the treatment of the four chronic diseases: hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus (type I and II) and depression, this study investigated the following research questions: (1) Were the proportion of patients 50 and over on methadone maintenance treatment treated with first-line agents comparable to the same demographic not on methadone maintenance treatment? (2) Of those on a first-line medication, was adherence comparable in the methadone maintenance

treatment group to the non-methadone maintenance treatment group?

Methodology

Research Design

A case-control research design was used to assess the associations between the treatment of chronic diseases and methadone maintenance treatment. Selection bias was minimized as cases and controls were randomly selected from the same secondary source (PharmaNet). In order to ensure comparability of the MMT group (cases) to the non-MMT group (controls), individual matching was used, where each case was individually matched with a control subject with the same characteristics. As the goal was to compare cases and controls having similar characteristics, this reduced confounding, and controlled for factors of age, sex, similar income level and local health area (LHA). Since prior research has shown that age and sex are related to the incidence of these study diseases, this case control approach ensured that the groups would be equivalent for these confounding factors between the groups and would not be attributable to any differences.

Data Source

In 1995, the British Columbia Ministry of Health introduced PharmaNet that links the province's community pharmacies, hospital outpatient pharmacies, emergency departments and medical practices to a common data-sharing network (Government of British Columbia., 2008). PharmaNet is an online, real-time province-wide network that captures prescriptions dispensed from all British Columbia community and hospital outpatient pharmacies and stores the

information on a central data system. British Columbia and Manitoba are currently the only provinces in Canada that have established province-wide medication management systems. Alberta and Saskatchewan, are in the process of implementing such a system and Newfoundland is in the planning phase. Ontario is the furthest behind as planning has not even started for a pharmacy management system to be implemented (Roszak, Zamora, & Ng, 2006). When a prescription is presented at the pharmacy, the pharmacist transmits the details of the prescription to PharmaNet. For long-term medications, the prescriber may indicate on the prescription the number of times the prescription may be dispensed (refills). The same prescription can be dispensed for the number of times that the prescriber authorized at the time the prescription was written. The maximum allowable dispensation for any medication covered under PharmaCare is a 100 days supply. For each medication dispensed, PharmaNet processes this information, which is then separated and recorded on to two separate tables, the MEDHIST and CLMHIST. Both the MEDHIST and CLMHIST store the following information: drug dispensed, patient, prescriber, pharmacy, pharmacist, date dispensed, quantity dispensed, days supply, and instructions for use. They differ in that the MEDHIST contains all prescriptions dispensed regardless of the payer whereas the CLMHIST contains all prescriptions where PharmaCare is the payer and excludes prescriptions for federally insured patients (e.g.; Status Natives, federal and provincial prisoners, Royal Canadian Mounted Police, and Canadian Armed Forces). The data obtained from PharmaNet is then stored in a data warehouse

that is approximately two weeks behind the real-time prescription dispensation. This data can be disclosed for research purposes. The PharmaNet Committee through the BC Ministry of Health currently manages the disclosure of this data. Data can be disclosed to the minister of health and to a person engaged in scientific or drug utilization research at a university or hospital or a person approved by the PharmaNet Committee for the purpose of conducting research. The data does not disclose the names or addresses of the patients and their practitioners. Only information contained in the CLMHIST data is available for research purposes. The PharmaNet committee works to protect the identity of patients, physicians and pharmacies while supplying complete quality data for approved purposes (Government of British Columbia., 2008). Names of patients, physicians and pharmacies were replaced with study ID's. Although the sex of the patient was released, the patients' birth dates were replaced with age, and the patients' local health area was the only level of geography that was released.

Sample Size

The sample size was calculated to be sufficiently large enough to detect moderate differences between the groups that would likely have clinical implications. The expectation was to detect small effect sizes with OR's under 0.5 or over 2. As there has been little research in this area, it was difficult to estimate a percentage that would be appropriate for all of the chronic diseases however, it was estimated that 20% in the MMT group and 28% in the non-MMT group were taking antihypertensive medications. These estimations were also used for the other study chronic diseases included in this study as the prevalence

of these diseases were less than hypertension in the same demographic. The estimate of 20% of the MMT group taking antihypertensive medications was based on the hypothesis that these patients may have poorer access to care, experience poorer chronic disease management secondary to stigmatization, and that there are still a considerable number of Canadians with untreated high blood pressure (59%) (Khan & Chockalingam, 2002). The 28% for the non-MMT group was taken from the prevalence of hypertension in BC in this age group (BC Ministry of Health, 2003). With 80% power (the standard) the sample size required was 85 for both groups in order to detect significant differences between groups (i.e. $p < .05$). Given the number of chronic diseases under investigation, the sample size had the potential to get very small for some subgroups (e.g., age by condition). This raised concern for the potential re-identification of study subjects with the PharmaNet Committee, and hence, 400 participants were agreed upon.

Study population

The cases consisted of 200 methadone maintenance patients, and the controls consisted of 200 non-methadone maintenance patients. Although methadone can be prescribed for pain control, the PharmaNet committee programmer was able to decipher between a patient on methadone maintenance treatment and methadone for pain control by the distinct product identification number (PIN) used to dispense the medication. The PIN for methadone maintenance involving direct patient interaction which can only be dispensed as a concentration of 1mg/ml is 66999990. In this instance the dispensing

healthcare professional must witness the patient ingesting the methadone. The PIN for methadone maintenance (1mg/ml) involving no direct patient interaction is 66999991. In this instance, the patient is not required to ingest the methadone in front of the healthcare professional. Methadone maintenance patients had to have a minimum of methadone dispensed equivalent to 15 days in any month during the study period.

Both groups included persons 50 years of age and older, who were residents of British Columbia at any time during Oct 1, 2008 to Dec 31, 2009, and had their prescriptions paid for under plan C coverage (social assistance) through BC's PharmaCare program. The age criterion of 50 was chosen because chronic disease prevalence rates increase with age. As prescription claims for federally insured patients are not available through CLMHIST, these patients were excluded. If any of the study subjects were incarcerated during the study period they would have been issued an incarcerated personal health number (PHN). Prescriptions dispensed to the incarcerated PHN are not linked to their PharmNet PHN. These prescriptions would not have been included in this data, and therefore, any study subjects that were included in this study, and incarcerated during the study period may have had missing data.

The PharmaNet committee programmer implemented the necessary criteria in order to randomly select the study population. In the reviewed studies, (see Table 1, page 19) there was a large variation of chronic disease prevalence rates, potentially indicating that the samples were not representative of the older MMT population. In this study, where the MMT patients were randomly selected

from a secondary source, the MMT sample was representative of persons in British Columbia with the same inclusion criteria.

Ethics

This study was approved by the University of Victoria's Ethics committee. The data released from the PharmaNet committee was limited to secondary analysis of anonymized data where the identity of the individuals could not be identified. The PharmaNet committee required an extensive application detailing the rationale for the data requested. This application was first examined by the PharmaNet Stewardship Secretariat Committee before being presented to the PharmaNet Stewardship Committee. Approval was granted by the PharmaNet Stewardship Committee in January 2011 for data extraction.

Measurement and Analysis

The data was received as seven files, many of which were in a hierarchal format that required transposition to a flat format, before being merged into a SPSS data file for analysis. Both the non-MMT and MMT groups had 3 files each: med_rpt.txt, med_chron, and med_acute. The med_rpt.txt file listed the participants that had a chronic study medication dispensed. The data included the following descriptions: unique study ID, date of birth, gender, date of service (Oct 1, 2008 to Dec 31, 2009), DIN/PIN (a unique 8 digit number to identify each medication), quantity, and days supply. Figure 1 shows an example of a hypothetical patient of how the data was displayed in the med_rpt.txt. file.

Figure 1: Example of data in the med_rpt. file

```
7564|192207|M|20081005|55999991|260|7  
7564|192207|M|20081122|55999991|260|7  
7564|192207|M|20081125|55999991|260|7  
7564|192207|M|20081203|55999991|260|7
```

The med_chron and med_acute files listed the unique study ID, date of birth, and sex of each participant. Only the counts of other chronic medications (not of interest in this study) and the counts of acute medications (short-term medications dispensed for less than 14 days in a month) dispensed for each participant were included in these respective files as the PharamaNet Committee did not release data that was not required for the analysis. Not every participant had a study chronic medication dispensed. The PharmaNet data analyst created these 3 files for both groups so that when these files were merged, there were

200 participants in both groups. For each case selected, a forward searching method was used to select a matched control subject (randomly ordered by prescription date i.e.: not sorted) to search for the first person who was of the same age, sex and resident in the same LHA. Although the 200 participants were established for both groups, as there were no common keys to merge and combine these files, the cases and controls were matched by birth date and sex (the LHA variable was not released i.e.: already included). The seventh file was the drug_list file which was required to identify the study chronic medication(s) that participants were dispensed. The seven variables listed were: GCN sequence number, AHFS, DIN/PIN, drug strength, dosage form, generic name and brand name.

In order to manage and organize the data, the MMT group (cases) were coded as “1” and numbered from 1 through 200 and the matched non-MMT group (controls) were coded as “0” and numbered from 1 through 200 by the data analyst. Males were coded as “1” and females were coded as “2”. All statistical analysis was conducted using SPSS version 19. Descriptive statistics were conducted first in order to ensure the integrity of the matching for age and sex, as well as summarizing the sample and measures. The average number of chronic study medications was then tabulated for both groups. For this count, generic code numbers (GCN's) were used to group all generically equivalent medications unique to its formulation, dosage form, route of administration and dose. GCN's were used for analyses instead of drug identification numbers (DINs). Since DINs are an eight digit number assigned by Health Canada that uniquely

identifies each drug product, using DINs for this count could have potentially introduced excess counts if different generic brands were dispensed for the same medication. The chronic medication DINs dispensed for each of non-MMT and MMT participants were recoded with their respective GCNs from the drug_list file in order for this count to occur. As well, the average number of chronic medication dispensations for each group was tabulated. Medications dispensed for acute conditions were not included in either (number of medications or dispensations) measure. Independent sample t-tests were conducted to assess whether the average ratios for both the number of medications each patient was taking, as well as the number of medication dispensations were significantly different between the groups for interval level data.

For each of the four diseases under investigation, the patients were counted if they had a first-line medication dispensed for greater than 2 weeks (in a month) for the particular disease at any time within the study period in MMT and non-MMT groups. As the data was not linked with MSP's billing information for diagnosis, the Ministry of Health's BC guidelines were used to look for first-line medications at their available or recommended doses. As the treatment of asthma can closely resemble COPD, a patient was only counted as being treated for COPD if the patient was on an anticholinergic alone or with a beta₂-agonist. For this count, the data analyst recoded all of the GCNs dispensed to both the non-MMT and MMT participants with the above mentioned stipulations from 1 through 4 (1=hypertension, 2=COPD, 3=diabetes and 4=depression), which was then compared with a manual count. Odds ratios were calculated using cross

tabulations in order to compare the odds of MMT patients to non-MMT patients on a first-line medication for each particular study disease. The variables of age, sex and LHA were controlled in the design of the study and therefore were not treated as covariates. Fisher's exact test was used to assess statistical significance for categorical data using 2x2 tables.

The adherence analysis was based on those participants with chronic study medication dispensations. In BC, patients can receive up to 3 months supply of medication(s) in one fill under the PharmaCare program. Several studies suggested that prescription claims adherence analysis requires greater than 3 months of data or 3 refills for a meaningful estimation (Andrade et al., 2006; Farmer, 1999; Grymonpre et al., 2006; Steiner & Prochazka, 1997). Consistent with these studies, and taking into account the number of months supply a patient can receive in one fill, 15 months of PharamaNet data was judged sufficient to calculate adherence measures. The PharmaCare data was recorded as a "days supply" variable calculated by the dispensing pharmacist instead of the actual dosage instructions. Although this variable increased the risk of error in adherence calculations especially for non-discrete dosage forms (inhalers and insulins in this study) where "take as needed or take as required" may have been the actual instructions, it was not feasible to obtain instructions on every prescription for this study. Many different definitions have been used by researchers to quantify adherence, however, a standardized definition has not been adopted. Even with studies using similar definitions, differences often existed in the calculations as well as the terminology (Andrade et al., 2006).

Continuous measure of medication availability (CMA) was chosen as the adherence measure for this study as CMA was amongst five other adherence measures: (continuous multiple interval measure of oversupply (CMOS), medication possession ration (MPR), medication refill adherence (MRA), continuous measure of medication gaps (CMG) and proportion of days covered (PCD) in a systematic review conducted by Hess et al (2006) that produced equivalent results for measuring prescription refill adherence, and had relatively fewer calculations than the other measures. CMA is the proportion of days supply obtained during a specified period of time. Depending on the “specified period of time” , there were two different calculations for this definition:

1) CMA(1)=

Sum of the days supply obtained (excluding last refill)

Total number of days between the first and last dispensing date x 100

2) CMA(2)=

Sum of days supply obtained during the observation period

Number of days of observation period x100

As adherence for the participants' persistent periods (continuous use periods), as well as for the entire study period were both of interest in this study, the above two calculations (CMA(1) and CMA(2)) were used to compare adherence measures between the groups. Like adherence, the term “persistence” had many definitions found in the literature. The literature considered persistence as having dispensations between 1 and 6 months after each dispensation (Andrade

et al., 2006). For example, if a prescription refill was due on day 30 but was not refilled until day 120 the patient would still be considered persistent. Taking this range into account, and that switching (to another medication) usually occurs within 4 months following the initial dispensation of a medication (Andrade et al., 2006), for CMA(1), dispensations were included within the same calculation even if a higher strength of the same medication was dispensed or if the patient was switched to a different medication within the same medication class as long as there were no gaps greater than 4 months between each dispensation. For both CMA(1) and CMA(2), if a participant was switched to another medication class, the stipulation of having 3 or more dispensations was in effect. Prescriptions extending beyond the end of the study period were truncated to the days supply at the end of the study period. Table 3 is an example of how the data was used to calculate CMA(1) for a hypothetical patient. Table 4 is an example of how the data was used to calculate CMA(2) for the same hypothetical patient. Depending on the definition and calculation of CMA used, these examples show that the results on the same participant can differ significantly.

Table 3: Example of CMA(1) calculation for a hypothetical patient

Dispensing Date (mm, day, yyyy) (A)	Cumulative Days in Interval (B)	Days Supply (C)	Cumulative Days Supply- Excluding Last Refill (D)	CMA(1) (E=D/B)
11/04/2008		30		
12/10/2008		30		
01/19/2009		30		
03/13/2009		40		
04/24/2009	171	30	130	0.76

Table 4: Example of CMA(2) calculation for the same hypothetical patient

Dispensing Date (mm, day, yyyy) (A)	Study Period in Days (B)	Days Supply (C)	Cumulative Days Supply (D)	CMA(2) (E=D/B)
11/04/2008		30		
12/10/2008		30		
01/19/2009		30		
03/13/2009		40		
04/24/2009	456	30	160	0.35

Adapting the definitions outlined by Grymonpre et al (2006), adherence “by patient” and by “medication class” was categorized as follows. CMA (by patient): Poor (at least one medication)=0 to 39%, poor high (at least one medication)=>120%, partial (at least one medication)=40 to 79%, and excellent (all medications)=80 to 119%. CMA (by medication class): Poor=0 to 39%, poor high=>120%, partial=40 to 79%, and excellent=80 to 119%. The means were calculated to compare the MMT and non-MMT groups for both CMA calculations “by patient” and “by medication class”. Independent t-tests were conducted in order to assess whether the means for both CMA’s “by patient” and “by medication class” were significantly different between the two groups.

Results

Once the coding was complete, it was discovered that control number 107 had methadone dispensed. Since the requirement for the control group was that individuals did not have any methadone dispensed for maintenance during the study period this subject along with the matched case were dropped from the analysis. The final total study population was therefore, 398, as pair number 107 was excluded from the analysis. Table 5 shows that of the 398 participants, 286 (71.9%) were men (143 in each group), 112 (28.1%) were women (56 in each group) . The participants' birthdates were subtracted from Aug 15, 2011 when the data was received to calculate a mean age of 59.4 years for both groups (see Table 6 and 7). Clearly, the matching process was conducted correctly.

Table 5: Distribution of the Groups by Sex

		Case-Control Status		TOTAL
		Controls (Non-MMT)	Cases (MMT)	
SEX	Male	143 (71.9%)	143 (71.9%)	286
	Female	56 (28.1%)	56 (28.1%)	112
TOTAL		199 (100%)	199 (100%)	398

Table 6: Age Characteristics

AGE	Case-Control Status		TOTAL
	Controls (Non-MMT)	Cases (MMT)	
54	9 (4.5%)	9 (4.5%)	18 (4.5%)
55	25 (12.6%)	25 (12.6%)	50 (12.6%)
56	22 (11.1%)	22 (11.1%)	44 (11.1%)
57	28 (14.1%)	29 (14.6%)	57 (14.3%)
58	21 (11.1%)	21 (11.1%)	42 (11.1%)
59	16 (8.0%)	15 (7.5%)	31 (7.8%)
60	17 (8.5%)	17 (8.5%)	34 (8.5%)
61	13 (6.5%)	13 (6.5%)	26 (6.5%)
62	7 (3.5%)	6 (3.0%)	13 (3.3%)
63	10 (5.0%)	12 (6.0%)	22 (5.5%)
64	7 (3.5%)	6 (3.0%)	13 (3.3%)
65	4 (2.0%)	4 (2.0%)	8 (2.0%)
66	6 (3.0%)	6 (3.0%)	12 (3.0%)
67	4 (2.0%)	4 (2.0%)	8 (2.0%)
68	1 (0.5%)	1 (0.5%)	2 (0.5%)
69	4 (2.0%)	4 (2.0%)	8 (2.0%)
70	1 (0.5%)	1 (0.5%)	2 (0.5%)
76	2 (1.0%)	2 (1.0%)	4 (1.0%)
78	1 (0.5%)	1 (0.5%)	2 (0.5%)
81	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 7: Mean Age

	Case/Control Status	N	Mean	Std. Deviation	Std. Error Mean
Age	Controls (non-MMT)	199	59.42	4.548	.322
	Cases (MMT)	199	59.42	4.545	.322

Table 8 illustrates the number of different medications that each patient was dispensed in both groups. Generally, there were more people in the MMT group that were on more than one chronic medication than the non-MMT group. The average number of study chronic medications dispensed for each patient was 0.65 (N=199) for the non-MMT group and 1.37 (N=199) for the MMT group as shown in Table 9. Equal variances was not assumed as Levene's test for equality of variances had a $p < 0.001$. A t-test showed the means were significantly different ($p < 0.001$).

Table 8: Number and percent of different medications dispensed for both groups

No. of Different Medications	Control (non-MMT group)	Case (MMT group)	Total
0	133 (66.8%)	103 (51.8%)	236 (59.2%)
1	33 (16.6%)	25 (12.6%)	58 (14.6%)
2	18 (9.0%)	25 (12.6%)	43 (10.8%)
3	7 (3.5%)	14 (7.0%)	21 (5.3%)
4	4 (2.0%)	16 (8.0%)	20 (5.0%)
5	2 (1.0%)	8 (4.0%)	10 (2.5%)
6	2 (1.0%)	1 (0.5%)	3 (0.75%)
7	0 (0%)	6 (3.0%)	6 (1.5%)
8	0 (0%)	0 (0%)	0 (0%)
9	0 (0%)	1 (0.5%)	1 (0.3%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 9: T-test Comparison of Cases and Controls for Average Number of Chronic Medications

Case/Control Status	N	Mean	Std. Deviation	Std. Error Mean	Sig (2-tailed)
# of Different Medications Controls (Non-MMT)	199	0.65	1.175	0.083	<0.001*
Cases (MMT)	199	1.37	1.878	0.133	

Note: *Equal variances was not assumed as Levene's test for equality of variances had a $p < 0.001$.

The average number of chronic medication dispensations that each patient received for the non-MMT group was 5.77 (N=199) and 27.88 (N=199) for the MMT group as shown in Table 10. The t-test was significant ($p < 0.001$).

Table 10: T-test Comparison of Cases and Controls for Average Number of Chronic Medication Dispensations

Case/Control Status	N	Mean	Std. Deviation	Std. Error Mean	Sig (2-tailed)
Total Chronic Dispensations Controls (Non-MMT group)	199	5.77	24.413	1.731	<0.001*
Cases (MMT group)	199	27.88	64.909	4.601	

Note: *Equal variances was not assumed as Levene's test for equality of variances had a $p < 0.001$.

Patients that had a first-line medication dispensed were counted for each of the four investigated diseases (see Tables 11 through 14). Overall, 66 (33.2%) participants in the non-MMT group and 96 (48.2%) in the MMT-group had a study chronic disease (see Table 15). Table 16 is a comparison of the odds ratios with the corresponding Fisher's exact test for significance between the two groups.

An odds ratio for COPD could not be calculated as there were no participants in the non-MMT group that had prescriptions filled to treat COPD. However, the statistical association for COPD by groups was significant ($p < 0.001$), indicating the cases were much more likely than the controls to have medications for COPD.

Table 11: Comparison of Medications for Hypertension Between Cases and Controls

Hypertension	Case/Control Status		Total
	Control (non-MMT)	Case (MMT)	
No	152 (76.4%)	157 (78.9%)	309 (77.6%)
Yes	47 (23.6%)	42 (21.1%)	89 (22.4%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 12: Comparison of Medications for COPD Between Cases and Controls

COPD	Case/Control Status		Total
	Control (non-MMT)	Case (MMT)	
No	199 (100.0%)	176 (88.4%)	375 (94.2%)
Yes	0 (0.0%)	23 (11.6%)	23 (5.8%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 13: Comparison of Medications for Diabetes Between Cases and Controls

Diabetes	Case/Control Status		Total
	Control (non-MMT)	Case (MMT)	
No	187 (94.0%)	190 (95.5%)	377 (94.7%)
Yes	12 (6.0%)	9 (4.5%)	21(5.3%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 14: Comparison of Medications for Depression Between Cases and Controls

Depression	Case/Control Status		Total
	Control (non-MMT)	Case (MMT)	
No	177 (88.9%)	131 (65.8%)	308 (77.4%)
Yes	22 (11.1%)	68 (34.2%)	90 (22.6%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 15: Comparison of Medications for Study Chronic Diseases Between Cases and Controls

Chronic Disease	Case/Control Status		Total
	Control (non-MMT)	Case (MMT)	
No	133 (66.8%)	103 (51.8%)	236 (59.3%)
Yes	66 (33.2%)	96 (48.2%)	162 (40.7%)
Total	199 (100%)	199 (100%)	398 (100%)

Table 16: Odds Ratios of Cases to Controls for Medications Related to 4 Chronic Diseases

Chronic Disease	OR	p-value (2-sided)	95% Confidence Interval	
			Lower	Upper
Hypertension	0.865	0.631	0.540	1.387
COPD	*	<0.001		
Diabetes	0.738	0.655	0.304	1.793
Depression	4.176	<0.001	2.455	7.103
All Study Chronic Diseases	1.878	0.003	1.252	2.817

Note: * could not be computed since no controls had a first-line treatment for COPD

Results of measures for adherence analysis for CMA(1) was based on 130 participants who were dispensed medications (non-MMT group=49, MMT group=81), 6296 dispensations (non-MMT group=1007, MMT group=5289), and 298 medications (non-MMT group=96, MMT group=202). As the criteria for the calculation of CMA(2) differed from CMA(1), results on measures for adherence analysis for CMA(2) was based on 139 participants (non-MMT group=55, MMT group=84), 6607 dispensations (non-MMT group=1120, MMT group=5487, and 325 medications non-MMT group=107, MMT group=218. Table 17 is a comparison of the participants' sex and mean age for the composition of CMA(1) and CMA(2) values.

Table 17: Comparison of Sex and Age for CMA(1) and CMA(2)

Participants	CMA(1)		CMA(2)	
	Non-MMT Group	MMT Group	Non-MMT Group	MMT Group
Men	35 (71.4%)	47 (58.0%)	39 (70.9%)	49 (58.3%)
Female	14 (28.6%)	34 (42.0%)	16 (29.1%)	35 (41.7%)
Total	49 (100.0%)	81 (100.0%)	56 (100.0%)	84 (100.0%)
Mean Age	58.7	59.3	58.5	59.3

Table 18 is a comparison of the number of participants in each group for both CMA(1) and CMA(2) calculations in the four different adherence levels. The MMT group in CMA(1) was the only group to have participants in the “poor high” level. As well, in both CMA(1) and CMA(2) the MMT group had a greater percentage of people in the “poor” adherence level and also had a lower percentage of participants in the “excellent” level in CMA(2).

Table 18: Comparison of adherence levels in both groups for CMA(1) and CMA(2)

Adherence Level	CMA(1)		CMA(2)	
	Control (non-MMT group)	Case (MMT group)	Control (non-MMT group)	Case (MMT group)
Poor (at least one medication) 0 to 39%	0 (0.0%)	3 (3.7%)	8 (14.5%)	24 (28.6%)
Poor high (at least one medication) >120%	0 (0.0%)	3 (3.7%)	0 (0.0%)	0 (0.0%)
Partial (at least one medication) 40 to 79%	11 (22.4%)	14 (17.3%)	23 (41.8%)	36 (42.9%)
Excellent (all medications) 80 to 119%	38 (77.6%)	61 (75.3%)	24 (43.6%)	24 (28.6%)
Total	49 (100.0%)	81 (100%)	55 (100%)	84 (100%)

The CMA(1) mean between the non-MMT group and the MMT group was not different (non-MMT group: 91.9%, SD 15.8, 95% confidence interval vs MMT group: 89.7%, SD 22.2, 95% confidence interval; using. The CMA(2) mean between the non-MMT group and the MMT group was statistically different (non-MMT group: 70.5%, SD 25.3, 95% confidence interval vs MMT group: 60.8%, SD 29.1, 95% confidence interval; Using Levene's test for equality (equal variances was assumed) $p=0.043$). The "by patient" CMA(1) mean was unexpected, as both groups were in the "excellent" level. The mean CMA(2) produced results that were more typical of the literature as both groups were in

the “partial” level. As the sex distribution of the groups differed as shown in Table 17 for CMA(2), (non-MMT group male=70.9%, female=29.1% vs MMT group male=58.3%, female=41.7%) and the groups were no longer matched for this analysis due to an unequal number of participants in each group on a study chronic medication, a univariate analysis of variance was conducted in order to determine if the CMA(2) mean between the two groups was significantly different after controlling for sex. Age was not controlled for as the mean age was similar in years between the two groups (Table 17 CMA(2) male=58.5, female=59.3). Sex was entered as the covariate, and the CMA(2) mean was the dependent variable. The MMT versus the non-MMT group status was still significantly related ($p<0.05$) to CMA(2) means while controlling for sex.

Table 19 is a comparison of CMA(1) and CMA(2), adherence “by medication class” for both groups where n in this case, was the number of medications included in the calculation. Again, adherence measured “by medication class” for CMA(1) was mainly in the “excellent” level for most oral medications except for inhalers and insulins which fell in the “partial” level for both groups. Whereas, adherence measured “by medication class” for CMA(2) showed varied results in that adherence on most medication classes for the non-MMT group were in the “partial” to “excellent” range, and adherence on most medication classes in the MMT group were either in the “poor” to “partial” range. Both CMA(1) and CMA(2) means for all medication classes were not significantly different (i.e: $p>0.05$) between the groups except for the calcium channel blocker medication class ($p<0.05$) in CMA(2). However, the chance that this difference

was significant in this medication class was probably small due to the small n's in both groups, particularly in the non-MMT group (n=4).

Table 19: Comparison of CMA(1) and CMA(2) by medication class

Medication Class	CMA(1)		CMA(2)	
	Control (non-MMT)	Case (MMT)	Control (non-MMT)	Case (MMT)
Diuretic	99.9% n=10	101.0% n=14	69.8% n=15	66.0% n=15
ACE Inhibitor	93.8% n=26	89.4% n=30	70.6% n=29	76.0% n=30
Ca ²⁺ Channel Blocker	95.9% n=4	93.2% n=10	85.7% n=4	31.9% n=12
Beta Blocker	97.0% n=7	100.8% n=13	70.4% n=8	68.1% n=13
Anticholinergic	N/A n=0	57.7% n=10	N/A n=0	30.3% n=15
SABA	N/A n=0	65.3% n=12	N/A n=0	41.3% n=15
Biguanide	91.4% n=8	84.1% n=3	75.4% n=8	71.0% n=3
Sulfonylurea	98.7% n=3	76.0% n=1	82.5% n=4	35.1% n=1
Insulin	74.8% n=6	64.2% n=13	63.4% n=7	41.6% n=13
Novel Action	96.4% n=12	105.1% n=32	67.9% n=13	69.5% n=33
SSRI	87.1% n=12	96.7% n=47	74.0% n=11	67.6% n=48
SNRI	92.6% n=8	86.8% n=17	72.7% n=8	62.6% n=20

n= Number of medications

Discussion

The results of this study were somewhat unexpected as it was hypothesized that the MMT group would have either higher or lower treatment in all four of the chronic diseases than the non-MMT group. The overall odds ratio (OR) was 1.878 ($p < 0.05$) for the MMT group to the non-MMT group for the pharmacological treatment of the chronic diseases examined in this study. However, when examining each chronic disease separately, hypertension and diabetes were treated less in the MMT group (OR for both < 1), however, these relationships were not significant. COPD and depression were treated significantly more often.

The odds ratios produced for hypertension and diabetes were likely attributable to a number of different factors: disease presentation, patient/physician behaviour, and MMT patient-specific limitations and risk factors. Both hypertension and type II diabetes are diseases that often do not present with any noticeable symptoms and instead are usually detected by clinical examination and laboratory testing. The diagnosis for hypertension requires that the patient sit quietly for 5 minutes before an inflatable cuff is wrapped around the upper arm by a clinician to take the patient's blood pressure (HealthLink BC, 2011). If the reading is high the clinician will likely require the patient to return for further visits to confirm the diagnosis. The diagnosis for both type I and type II diabetes requires that a clinician draw blood from the patient to be analyzed at a lab. Patients may also have stipulations on timing of their last meal depending on which test is conducted. Again, further follow-up visits may be required to

confirm the diagnosis. The diagnosis and follow-up for both of these diseases require actions by both the patient and clinician that could prove inconvenient especially for the older MMT patient. Older MMT patients may have poorer access to transportation required to get to and from appointments, reduced mobility due to limited physical functioning from the toll that drug addiction has taken (Millson et al., 2004), and poorer cognitive function associated with accelerated aging from decades of substance dependence (Rosen et al., 2010). The above impediments specific to older MMT patients may have reduced the likelihood of this group seeking care.

Even if prescription medications were necessary for either of these diseases, patients may have been reluctant to take these medications. With the exception of uncontrolled type I diabetes, patients with hypertension and type II diabetes usually do not experience symptoms and may not believe or understand the necessity of taking medications to prevent future consequences of the diseases. In addition, patients may have been concerned about potential side effects. Many of the antihypertensive and oral diabetic medications do not provide immediate or noticeable results and can actually make a patient feel worse for the first few weeks until the body habituates. For many older MMT patients that are generally already in worse overall health than equivalent age population norms (Rosen et al., 2008), incentive to take these medications could have been lacking. As well, in this study, some of the participants in the MMT group that were on a chronic study medication took a greater number of different medications than the non-MMT group during the study period that may have lead

to difficulty in managing multiple regimens. Eventually, if either of these diseases is left untreated, they run the risk of increased morbidity and mortality, resulting in hospitalizations and potentially death. With hospitalization due to disease progression, older MMT patients usually have longer and more costly hospital stays compared to the general population due to their poor baseline health (Popova et al., 2005).

The findings in this study that 21.1% of the MMT participants had hypertension and 4.5% had diabetes were much lower than in the literature. The studies reviewed found that 44.9% to 62.3% of MMT patients had hypertension and 11.4% to 43.0% had diabetes (Rosen et al., 2010). However, these studies were conducted in substance dependent treatment facilities providing integrated care, meaning that participants had access to a wide variety of services on-site (e.g.: primary care, counseling, outreach workers, lab work etc.). With on-site access to primary care services, MMT patients may have had a better opportunity to be screened and tested for these diseases, potentially explaining the higher prevalences. In BC, integrated services with other health and social systems of care and welfare accommodating the complex needs of MMT patients are still rare (Parkes & Reist, 2010). Outpatient clinicians working in substance abuse treatment facilities in BC are in a key position to screen for and treat chronic diseases such as hypertension and diabetes, as MMT patients are seen at least monthly for their methadone prescription. Unfortunately these facilities are often poorly resourced environments that cannot afford to offer integrated services, as services are already limited to begin with (Parkes & Reist, 2010).

Like the ORs seen with hypertension and diabetes, the results of the large ORs produced for COPD and depression may be interpreted by considering: disease presentation, patient and physician behaviours, and MMT patient specific risk factors. Both COPD and depression produce noticeable symptoms for which patients may seek medical attention and treatment. Symptoms for COPD include one or more of the following: a productive cough, shortness of breath, wheezing, frequent lung infections, feeling tired, and unintentional weight loss (The Canadian Lung Association, 2009). Symptoms of depression include experiencing a depressed mood or loss of pleasure and at least 4 of the following symptoms: sleep disturbance, reduced interest, guilt/self blame, energy loss/fatigue, concentration problems, appetite change, psychosocial changes and suicidal thoughts for at least 2 weeks (Hahn et al., 2006). A spirometry test is used to diagnose COPD. This test requires that the patient blow into a mouthpiece connected to a machine to determine lung function, and can be readily conducted in a doctor's office. Depression is diagnosed by history taking which clinicians already do as part of their interaction with patients during appointments. For both of these diseases, symptoms would be easily recognized during a routine visit for a refill methadone prescription, and diagnosis requires less action by both the patient and clinician.

As for treatment, clinicians may have more readily prescribed treatments for both of these diseases and patients may have been more apt to taking these medications because they were not feeling well. First-line medications prescribed for either of these diseases provides symptom relief either instantly

(inhalers for COPD) or within a few weeks (antidepressants). Side effects from inhalers usually go away within a few minutes and are more related to the delivery of the medication (e.g.: aerosol hitting the back of mouth due to poor aim leading to hoarseness and sore throat) rather than the actual medication itself. There are many side effects for antidepressants. However, many patients do not usually experience any serious side effects (rare) and most can be managed or abate after the initial period. For many of the MMT patients in this study, taking medications that offered immediate benefit might have been more appealing.

Smoking is the biggest risk factor for COPD. Although the participants' current cigarette (nicotine) smoking habits could not be determined in this study, 3 of the studies reviewed reported that 84.1% to 87.1% of older MMT patients smoked during the study periods. Given that there is a high prevalence of smoking in older methadone patients, the finding that 11.6% of the MMT participants in this study were treated for COPD was consistent with the range found in the reviewed studies (2.4% to 36.4%). Screening for COPD may have also been higher in the MMT group because of the high prevalence of smokers in this population that may have aided in diagnosis and treatment. It was unexpected that in this study, the non-MMT group had zero participants treated for COPD as according to the BC Tobacco report (2008), 17.2% of the BC population over 45 years and 9.3% over 65 smoked. Although this rate was much lower than that found in older MMT patients from the literature, one cannot conclude from the results that the non-MMT group in this study did not have

COPD. Possible explanations for the zero participants treated for COPD in the non-MMT group are discussed in the limitations section.

Risk factors for depression are more complex and patient specific. With life-long opioid dependence, age often changes the roles that older MMT patients may have previously had both within the drug culture and mainstream society (Rosen et al., 2010). For example, older MMT patients may have decreased participation in the drug culture due to poorer health-related quality of life and lower rates of substance use than their younger counterparts (Loftwall et al., 2005). With this decreased participation, status is lost within their social circles and the older MMT patients are pushed to the outer edges of their own society. As social relationships are lost, they often become lonely, isolated and marginalized (Rosen et al., 2010). As well, older MMT patients have many other risk factors for depression. For example: substance dependence, physical comorbidities, psychological/physical trauma and other psychiatric disorders. In this study, the finding that 34.2% of the MMT participants were receiving pharmaceutical treatment for depression was consistent with the reviewed literature (32.9% to 34.1%).

The adherence analysis presented a comparison between the MMT to the non-MMT group using two different calculations for CMA. Both CMA(1) and CMA(2) were only calculated on medications with 3 or more dispensations that amounted to a minimum of 14 days. For CMA(1) this stipulation resulted in excluding 32 participants (non-MMT=17 and MMT=15), 402 dispensations (non-MMT=142, MMT=260) and 103 medications (non-MMT=33, MMT=70). For

CMA(2) this stipulation resulted in excluding 23 participants (non-MMT=11, MMT=12), 91 dispensations (non-MMT=29, MMT=62) and 76 medications (non-MMT=22, MMT=54). Using three or more refills minimized the exaggerated CMA values that can occur with using only two dispensations and allowed for a longer assessment of adherence behaviour (Grymonpre et al., 2006).

During persistent periods, the “by patient” comparison between the non-MMT and MMT group for CMA(1) were comparable (non-MMT=91.9% vs MMT=89.7%). A possible explanation could be due to the number of dispensations. The average number of chronic medication dispensations of the MMT group (27.88) compared to the non-MMT group (5.77) suggests that the MMT group had smaller quantities dispensed and frequented the pharmacy more often than the non-MMT group. For the MMT group, frequent interaction with pharmacy staff (due to methadone ingestion in front of the pharmacist) may have contributed to prompting refills and closer monitoring for compliance on the chronic medications (Wertheimer & Santella, 2003). Also, during persistent periods, participants may have been more motivated to fill these prescriptions, as persistence is usually better in the first six months of treatment for chronic diseases (Osterberg & Blaschke, 2005). However, looking at adherence during the entire study period “by patient” in CMA(2) the MMT group had significantly lower adherence (non-MMT=70.5% vs MMT=60.8%, $p<0.05$). The major predictors of poor adherence to medications are: presence of psychological problems especially depression, cognitive impairment, treatment of asymptomatic disease, side effects of medication(s), poor belief of treatment/lack

of insight to disease, complex regimen, and poor follow-up/barrier to care/missed appointments (Osterberg & Blaschke, 2005). Depression was more prevalent in the MMT group than non-MMT group in this study (34.2% vs 11.1%). As well, many of the predictors related to poor adherence may have especially affected the MMT group, which could have explained the lower adherence rate in this group. Over time, after the first six months, when patients are treated for chronic conditions, adherence rates have been found to decline (Dunbar-Jacob et al., 2000). For both groups, it was unclear whether non-adherence was caused by actual patient non-adherence, nonpersistence, hospitalization, time away from the province, data entry error, time in federal prison, free samples from the doctor replacing usual therapy, or drug discontinuation ordered by a physician (Grymonpre et al., 2006) as PharmaNet does not capture any of these scenarios.

Neither CMA(1) or CMA(2) produced significant differences between the groups “by medication class” due to the small number of medications in each medication class. However, it was interesting to note that in CMA(2), insulins were quite a bit lower in the MMT group (non-MMT=63.4% vs MMT=41.6%). Although a comparison could not be made for inhalers between the two groups because zero prescriptions were dispensed for COPD in the non-MMT group, overall, inhalers and insulins tended to rate the lowest in terms of adherence (30.3% to 41.6%). Both of these medication types require a device to deliver the medication (aerosol canisters for inhalers, and injections for insulins) that could be cumbersome as well as harder to use than swallowing a medication. Both usually have to be used multiple times a day (complex regimen), and usually

require dosage adjustments throughout the day depending on symptoms, physical activity, or blood glucose readings. Many of these factors require lifestyle organization that may have been lacking in the MMT group resulting in the lower adherence to these medication types. The different adherence results produced for CMA(1) and CMA(2) in this study showed that adherence was dependent on the definition and calculation used.

Utilizing PharmaNet data for this research was feasible, however, future researchers should carefully consider time lines, and funding before applying for such data. The extensive application process for PharmaNet data required many discussions with the PharmaNet Stewardship Secretariat Committee (responsible for supporting both the researcher and the PharmaNet Stewardship Committee) to clarify the exact description of the data required once the application was submitted. This clarification of the application took 5 months prior to being considered in its final format and ready for review by the PharmaNet Stewardship Committee. Final approval was granted 2 months later. It then took a further 5 months to obtain the estimated cost for the data extraction. Up to that point, no information could be provided regarding the cost of this data extraction. Approval of the cost (\$2,900) was required before the data extraction could commence. The initial inclusion criteria for the MMT group stipulated that patients in this group had a minimum of methadone dispensed equivalent to 15 days per month during the entire study period. This was in an effort to include MMT patients who had regular contact with a clinician who could potentially also treat comorbid chronic diseases that could have strengthened the association of the increased

or decreased likelihood for being treated for the study chronic diseases. However, this criteria only produced 25 patients, and therefore the inclusion criteria had to be amended to produce the required study population. The revised inclusion criteria had to be re-approved by the PharmaNet Stewardship Committee. Once approval was granted, data extraction took 2 months. From start to finish, the entire data extraction process took 15 months.

This study was not linked to the BC Ministry of Health's physician services. This would have allowed for correlation of the diagnostic code for the chronic disease associated with the appropriate indicated medication. Unfortunately, this was not feasible as the extraction of this study's data was over budget, and coordinating the data extraction from the PharmaNet Committee and Population data BC (for the diagnostic codes) would have exceeded the time constraints for this project. However, the analysis was conducted adopting conservative assumptions biased against more evidence-based effective treatment.

Limitations

There were three areas that affected this study and its limitations: study design, PharmaNet data, person behaviour. The potential biases that could have occurred due to the study design were carefully considered. It was possible that there was significant heterogeneity within the MMT group such as time on treatment, dose of methadone, access to services, Pharmacare eligibility, other chronic diseases, mental health, race, marital status and other supports, etc. Although there were 1700 MMT patients over 50 in 2009 in BC, those that met

the inclusion criteria for this study was only 240. Randomization was still conducted however, generalizability must be considered by this limitation. Some of these heterogeneous factors could have also been present between the two groups that could have impacted this study. Unfortunately, not all potential confounding factors could be controlled for in this study. For example, those who were married may have had more encouragement to seek help for symptoms of diseases. The groups could have been very different for this variable. However, as participant selection procedures were the same for cases and controls (randomly matched from the PharmaNet database), potential biases were likely minimal. Information bias that could have affected classification and measurement was also very low in this study. As interviews were not conducted and cases and controls were selected from anonymized data, misclassification of the study participants was low, and non-response bias was not applicable. Although this type of study design cannot prove causation on its own, this was an innovative study suggestive of the direction for future studies.

Another limitation was that the data obtained from PharmaNet was only as accurate as what was entered by the user. It was important that the user selected the correct Product Identification Number (PIN) in order to separate the patients taking methadone for pain and those taking it for maintenance. This was a fairly minor limitation as this bias would have applied to both cases and controls equally. The PharmaNet system also performs data-quality checks to flag when prescriptions are processed (Dormuth et al., 2008) and as a result, misclassification in this study should have been very low. As PharmaNet data

provides information regarding claims history, this method is indirect and cannot confirm medication consumption. Although PharmaNet may not capture how frequently/infrequently or inconsistently medication(s) were taken in between fills, this method has been deemed valid by several studies (Dahri et al., 2008; Farmer, 1999; George & Shalansky, 2006; Grymonpre et al., 2006; Steiner & Prochazka, 1997). As instructions of use for each medication was not released, the “days supply” measure was used. Using this measure can potentially over or underestimate adherence as some medications are prescribed “as needed” especially in the case of non-discrete dosage forms (inhalers and insulins in this study) which could have impacted the adherence calculations.

This study did not take into account those persons that obtained a prescription for a first line agent but chose not to fill it. As PharmaNet does not capture prescriptions dispensed in a hospital, those patients were not included in the study. Patients receiving medications from a hospital are likely to suffer from health problems which requires immediate attention and often do not represent the general population. As well, PharmaNet does not include data for prescriptions dispensed to federally insured patients. Since these patients only account for a small portion of the total population (4%) excluding them should not have substantially affected the results (Dormuth et al., 2008). This study did not take into account those patients that may have previously tried first-line medications and had to be switched, or those who were initiated with treatment from a second or third-line agent. Finally, as the cases were only representative of persons aged 50 and over, captured on PharmaNet, covered by PharmaCare,

with an opiate addiction treated with methadone, the generalizability of the results will only be applicable to those with the same characteristics.

CONCLUSIONS

The results from this study showed that MMT patients had similar treatment for hypertension and diabetes than the non-MMT group. For COPD and depression however, treatment was significantly more likely for the MMT group than the non-MMT group. During patients' persistent periods, adherence did not differ between the groups, however, over a period of 15 months, the MMT group had significantly lower adherence rates than the non-MMT group. As the odds ratios for the treatment of all four chronic diseases differed, it may be worthwhile to look at each chronic disease separately to suggest potential targets for intervention. Disease-specific tailored interventions related to lifestyle risk factors (e.g.: smoking, long-term opioid dependence), comorbid medical conditions, and adherence to chronic medications could potentially improve the overall health of older MMT patients. However, development of appropriate interventions and treatments for older MMT patients requires research that properly recognizes the physical and mental health problems faced by these patients (Rosen et al., 2010). Some chronic diseases occurring later in life for example thyroid conditions, heart conditions, arthritis and osteoporosis may be exacerbated by life-long opioid dependent lifestyles (Rosen et al., 2010). These diseases warrant further investigation as symptoms may be less pronounced at the start of the disease, and screening and treatment may be more limited to the older MMT patient due to poor access to care. Unfortunately in BC, a patient's MMT doctor may not be their primary care doctor. Outpatient MMT programs require frequent patient attendance both with the doctor and pharmacist. This

offers a rare opportunity to address the physical and mental health problems faced by patients on-site. An integration of coordinated care along with validated tools for the evaluation of these physical and health problems are needed (Rosen et al., 2010).

In 2009, the College of Physicians and Surgeons of British Columbia reported 10,098 MMT patients (3533 female and 6565 male) with approximately 60% of these patients between the ages of 31 and 50, and 17% over the age of 50. In light of the age of the participants in this study, along with the aging MMT demographic trend, there will likely be an increase in the number of older MMT patients in the province over the next decade. The public health cost of poor identification, prevention and/or treatment of potential risk factors for younger older MMT patients make them susceptible for additional burdens as they age (Rosen et al., 2010). The older demographic will potentially place greater financial burden on a health care system that is already struggling to stay financially afloat. One of the goals of healthcare in Canada is to reduce disease burden and suffering for all citizens and this includes those with opioid dependence.

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Appendices

Appendix 1: First-Line Antihypertensive Medications Available in BC

DRUG CLASS AND NAME	AVAILABLE DOSE	PHARMACARE BENEFIT
THIAZIDE DIURETIC		
Hydrochlorothiazide	12.5mg, 25mg, 50mg	Yes
Indapamide	1.25mg, 2.5mg	Special Authority Required
ANGIOTENSIN CONVERTING ENZYME (ACEI)		
Quinipril (Accupril®)	5mg, 10mg, 20mg, 40mg	Yes
Ramipril (Altace®)	1.25mg, 2.5mg, 5mg, 10mg	Yes
Captopril (Capoten®)	6.25mg, 12.5mg, 25mg, 50mg, 100mg	Yes
Cilazapril (Inhibace®)	1mg, 2.5mg, 5mg	Yes
Trandolapril (Mavik®)	1mg, 2mg, 4mg	Yes
Enalapril (Vasotec®)	2.5mg, 5mg, 10mg, 20mg	Partial
Lisinopril (Prinivil®, Zestril®)	5mg, 10mg, 20mg	Partial
BETA-BLOCKERS		
Atenolol (Tenormin®)	25mg, 50mg, 100mg	Yes
Metoprolol (Lopressor®, Betaloc®)	25mg, 50mg, 100mg	Yes
Propranolol	10mg, 20mg, 40mg, 80mg, 120mg	Yes
DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKER (DHP-CCB)		
Felodipine (Renedil®)	2.5mg, 5mg, 10mg	Yes
Nifedipine (Adalat® XL)	20mg, 30mg, 60mg	Yes
Amlodipine (Norvasc®)	5mg, 10mg	Partial

Appendix 2: First-line COPD Medications Available in BC

DRUG CLASS AND NAME		AVAILABLE DOSE	PHARMACARE BENEFIT
SHORT ACTING BETA ₂ AGONIST INHALED (SABA)			
Salbutamol	Airomir™, Ventolin®	100ug/dose MDI	Yes
	Ventolin® Diskus®	200ug/dose	No
	Ventolin Nebules	2.5mg/2.5ml Solution	Special Authority Required
Terbutaline	Bricanyl®	0.5mg/dose	Yes
SHORT ACTING ANTICHLINERGIC (SAAC)			
Ipratropium	Atrovent®	20ug/dose MDI	Yes
	G Nebules	500ug/ml Solution	Special Authority Required

Appendix 3: Insulin Treatment Types Available in BC

NAME	PHARMACARE BENEFIT
Humalog®	Partial
NovoRapid®	Partial
Humulin® R	Yes
Novolin® ge Toronto	Yes
Humulin®-N	Yes
Humulin®-L	Yes
Novolin®ge NPH	Yes
Humulin®-U	Yes
Lantus®* (insulin glargine)	Partial
Humalog® Mix25™	Partial
Humulin® (20/80, 30/70)	Yes
Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50)	Yes
NovoMix® 30	Partial

Appendix 4: Oral First-line Medications for Type II Diabetes Available in BC

DRUG CLASS AND NAME	AVAILABLE DOSE	PHARMACARE BENEFIT
ALPHA-GLUCOSIDASE INHIBITOR		
Acarbose (Prandase®)	50mg, 100mg	Yes
BIGUANIDE		
Metformin (Glucophage®)	500mg, 850mg	Yes
INSULIN SECRETAGOGUES SULFONYLUREAS		
Gliclazide (Diamicon®, Diamicon® MR)	30mg MR, 80mg	Special Authority Required
Glimepiride (Amaryl™)	1mg, 2mg, 4mg	No
Glyburide (Diabeta®, Euglucon®)	2.5mg, 5mg	Yes
INSULIN SECRETAGOGUES NONSULFONYLUREAS		
Nateglinide (Starlix®)	60mg, 120mg	No
Repaglinide (GlucoNorm®)	0.5mg, 1mg, 2mg	No
INSULIN SENSITIZERS (TZDS)		
Pioglitazone (Actos®)	15mg, 30mg, 45mg	Special Authority Required
Rosiglitazone (Avandia®)	2mg, 4mg, 8mg	Special Authority Required

Note: Chlorpropamide and Tolbutamide are still available in Canada, but rarely used.

Appendix 5: First-Line Antidepressants Available in BC

DRUG CLASS AND NAME	AVAILABLE DOSE	PHARMACARE BENEFIT
NOVEL ACTION		
Bupropion-SR (Wellbutrin® SR, Wellbutrin® XL)	150mg, 300mg	Special Authority Required
Mirtazapine (Remeron®)	15mg, 30, 45mg	Yes
Trazodone (Desyrel®)	50mg, 100mg, 150mg	Yes
REVERSIBLE MONOAMINE OXIDASE INHIBITOR (RIMA)		
Moclobemide	100mg, 150mg, 300mg	Yes
SERATONIN AND NOREPINEPHRINE REUPTAKE INHIBITOR (SNRI)		
Venlafaxine-XR (Effexor® XR)	37.5mg, 75mg, 150mg	Yes
SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI)		
Citalopram (Celexa®)	10mg, 20mg, 40mg	Yes
Fluoxetine (Prozac®)	10mg, 20mg	Yes
Fluvoxamine (Luvox®)	50mg, 100mg	Yes
Paroxetine (Paxil®)	10mg, 20mg, 40mg	Yes
Sertraline (Zoloft®)	25mg, 50mg, 100mg	Yes