Methadone Program

Methadone Maintenance Treatment
Program Standards and Clinical Guidelines

4th Edition February 2011

THE COLLEGE OF PHYSICIANS & SURGEONS OF ONTARIO

These guidelines are in effect as of February 2011

Wade Hillier
Associate Director, Practice Enhancement and Assessment
College of Physicians and Surgeons of Ontario
80 College St., Toronto, Ontario M5G 2E2
Telephone: (416) 967-2661
Email: whillier@cpso.on.ca

The College of Physicians and Surgeons of Ontario

Vision Statement

Quality Professionals, Healthy System, Public Trust

Our Mandate

Build and maintain an effective system of self-governance.

The profession, through and with the College, has a duty to serve and protect the public interest by regulating the practice of the profession and governing in accordance with the Regulated Health Professions Act.

Our Vision Defined

Quality Professionals, Healthy System, Public Trust.

Our new vision is the framework by which we organize ourselves.
It guides our thinking and actions into the future. It defines not only who we are, but what we stand for, the role we see for ourselves, our critical relationships, in what system we work, and the outcomes we seek.

Each component of our vision is defined below:

Quality Professionals – as a profession and as professionals, we recognize and acknowledge our role and responsibility in attaining at a personal, professional, and at a system-level, the best possible patient outcomes.

We are committed to developing and maintaining professional competencies, taking a leadership position on critical issues that impact the performance of the system, and actively partner to provide tools, resources, measurement, to ensure the optimal performance at all levels of the system.

Healthy System – the trust and confidence of the public and our effectiveness as professionals is influenced by the system within which we operate. Therefore, we, as caring professionals, are actively involved in the design and function of an effective system including:

- accessibility
- the interdependence of all involved
- measurements and outcomes
- continued sustainability

Public Trust – as individual doctors garner the trust of their patients, as a profession we must aim to have the trust of the public by:

- building positive relationships with individuals
- acting in the interests of patients and communities
- advocating for our patients and a quality system

Our Guiding Principles

Integrity, accountability, leadership and cooperation

The public, through legislation, has empowered the profession to regulate itself through the College. Central to the practice of medicine is the physician-patient relationship and the support of healthy communities. As the physician has responsibility to the patient, the profession has the responsibility to serve the public through the health-care system.

To fulfill our vision of quality professionals, healthy system, public trust we will work to enhance the health of the public guided by professional competence and the following principles:

Integrity – in what we do and how we go about fulfilling our core mandate:

- Coherent alignment of goals, behaviours and outcomes;
- Steadfast adherence to a high ethical standard.

Accountability to the public and profession – we will achieve this through:

- An attitude of service;
- Accepting responsibility;
- Transparency of process;
- Dedicated to improvement.

Leadership – leading by proactively regulating our profession, managing risk and serving the public.

Cooperation – seeking out and working with our partners – other health-care institutions, associations and medical schools, etc. – to ensure collaborative commitment, focus and shared resources for the common good of the profession and public.

TABLE OF CONTENTS

Tables

Note: Throughout this document, Standards and Guidelines refers to *"MMT Program Standards and Clinical Guidelines".*

ACRONYMS

AA	Alcoholics Anonymous
AMA	Against Medical Advice
BZD	Benzodiazepine
CA	Cocaine Anonymous
CAGE	Cut-Down, Annoyed, Guilty, Eye-Opener Test
CAMH	Centre for Addiction and Mental Health
CBT	Cognitive Behavioural Therapy
CFPC	College of Family Physicians of Canada
CHC	Community Health Centre
CIHC	Canadian Interprofessional Health Collaborative
CNCP	Chronic Non-Cancer Pain
CNS	Central Nervous System
COPD	Chronic Obstuctive Pulmonary Disease
COWS	Clinical Opiate Withdrawal Scale
CPSO	College of Physicians and Surgeons of Ontario
CSC	Correctional Services of Canada
CWU	Chemical Withdrawal Unit
ECG	Electrocardiogram
EDDP	2-Ethylidene-1, 5 Dimethyl-3, 3-Diphenylpyrrolidine
EIA	Enzyme Immunoassay
EMIT	Enzyme Multiplied Immunoassay Technique
GAC	Guideline Advisory Committee
GHN	Growth Hormone Normal
HCV	Hepatitis C Virus
HIV/HCD	Humuan Immunodeficiency Virus
IPC	Inter-Professional Collaboration
LAAM	Levo-Alpha Acetyl Methadol
MI	Motivational Interviewing
MMT	Methadone Maintenance Treatment
MOHLTC	Ministry of Health and Long-Term Care
NA	Narcotics Anonymous
NAS	Neonatal Absence Syndrome
OAT	Opioid Agonist Therapy
ODT	Opiod Dependence Treatment
OCP	Ontario College of Pharmacists
OTN	Ontario Telemedicine Network
PAG	Patient Advisory Group
PHIPA	Personal Health Information Protection Act
PO	
POATS	Prescription Opioid Addiction Treatment Study
RCT	Randomized Controlled Trials
R.N.	Registered Nurse
SAMSHA	Substance Abuse and Mental Health Services Administration
TCA	Tricylic Antidepressant
THC	Tetrahydrocannabinol
TM	Telemedicine
UDS	Urine Drug Screen

1. Preface

1.1 Role of the CPSO in MMT

In 1996, the College of Physicians and Surgeons of Ontario (CPSO; the CPSO) began to administer a methadone program on behalf of the Ministry of Health and Long-Term Care (MOHLTC). The program goal is to improve the quality and accessibility of methadone maintenance treatment (MMT) in Ontario. This goal is achieved in cooperation with the Centre for Addiction and Mental Health (CAMH), and the Ontario College of Pharmacists (OCP). The profile of MMT in Ontario has been enhanced through outreach activities and the recruitment of physicians to prescribe methadone in the treatment of opioid dependence.

The CPSO is the body that regulates the practice of medicine to protect and serve the public interest. This system of self-regulation is based on the premise that the CPSO must act first and foremost in the interest of the public. *(www.cpso.on.ca)*

The Methadone Committee was established in June 1999 by the CPSO Council. The by-law states that the Committee shall administer the CPSO's methadone opioid agonist program, including:

- Brief programs of education in addiction medicine
- The establishment of guidelines or standards applicable generally to the use of opioid agonists in the management of opioid dependence
- A program to review prescribing opioid agonists by members in the management of opioid dependence; and
- Decision to issue or refuse to issue, or withdraw the exemption for a member to administer, prescribe or otherwise furnish opioid agonists for the management of opioid dependence

The Committee comprises physician and public members of the CPSO Council, non-Council members, and MMT physicians. Representatives of CAMH and the OCP are observer members. The Committee is subject to the Rules of Governance established by the CPSO Governance Committee.

1.2 Role of the Guideline Advisory Committee

The role of the Guideline Advisory Committee (GAC) is to update the 2005 Methadone Maintenance Treatment Guidelines. The GAC has been given the responsibility to ensure clarity around what will be considered "standards of practice" and those which are considered "best practice guidelines".

This document replaces the CPSO 2005, 2001, and 1996 MMT Guidelines, and Health Canada's *"The Use of Opioids in the Treatment of Opioid Dependence,"* published in 1992.

It is acknowledged that other healthcare professionals are involved in the care of opioid dependent patients. However, the intended audience for this document is MMT physicians. It is not intended as a comprehensive manual or to replace sound clinical judgment.

1.2.1 Guideline Advisory Group Members

Dr. Sharon Cirone, Chair, Community and Hospital-Based MMT Physician
Ms Nicole Balan, Ontario College of Pharmacists (OCP)
Ms Betty Dondertman, Centre for Addiction and Mental Health (CAMH)
Dr. Trevor Gillmore, Methadone Committee Member
Dr. Kumar Gupta, College of Physicians and Surgeons of Ontario Council Member
Ms Jan Holland, Correctional Services Canada (CSC)
Dr. Meldon Kahan, Methadone Committee Member and Hospital-based MMT Physician
Dr. Melissa Snider-Adler, Methadone Assessor
Mr. Sean Winger, Patient Advisory Group Member (PAG)

Note: The Guideline Advisory Committee members wish to acknowledge the contribution of Dr. Alice Ordean who provided the entire content for Section 13, MMT Considerations During Pregnancy and Dr. Anita Srivastava for her contribution to Section 12, Methadone Toxicity.

1.3 Role of the Research Advisory Group (RAG)

The Research Advisory Group was formed to work collaboratively with the Guidelines Advisory Group to complete the 2011 revision of the MMT Guidelines.

The primary role of the Research Advisory Group was to conduct a focused literature search to address specific questions, select and appraise the relevant literature and synthesize the evidence to assist the Guideline authors. Their secondary role was to review the program standards ands guidelines content created by the authors and ensure that:

- references cited in the program standards and guidelines were appropriate, i.e., they appropriately and adequately supported the material they were linked to,
- statements in the program standards and guidelines which required referencing were appropriately referenced, and,
- references from the focused literature search were used appropriately in the program standards and guidelines.

1.3.1 Research Advisory Group Members

Dr. Bruna Brands PhD., Team Lead, Office of Drug and Alcohol Research and Surveillance, Health Canada
Ms Sheila Lacroix, Senior Reference Librarian, Centre for Addiction and Mental Health
Dr. Thea Weisdorf, Physician Consultant and MMT Physician
Mr. Christopher Smith PhD., Research Assistant
Ms Gabriela Novotna, PhD, Research Assistant
Mr. Vlad Kushnir, MSc., Research Assistant

The Research Advisory Group also received support and advice from the College's Research and Evaluation Department.

1.4 Standards and Guidelines

Standards are regarded as generally accepted principles of patient management. Standards are based on a synthesis of current literature and a high level of consensus among the Guideline Advisory Committee. Standards are differentiated from Guidelines in that they refer to clinical practices that potentially relate to patient morbidity and mortality and to community safety. Standards may be modified only under exceptional circumstances and where the reasons for departure from the standards are clearly documented.

Guidelines are systematically developed recommendations and educational references that assist the MMT physician in making clinical decisions about patient care. Clinical guidelines are recommendations that are supported by a synthesis of current literature and clinical consensus. Guidelines may be adopted, modified, or rejected according to clinical needs, individual patient considerations, local resources, and physician discretion. Guidelines do not establish inflexible protocols for patient care nor are they meant to replace the professional judgment of physicians.

1.4.1 Evidence Synthesis Methods

In preparation for revision 2011, a mixed methods approach was decided upon, i.e. a blend of expert opinion (Guideline Advisory Committee) and evidence synthesis from a focused literature search. Limited time and resources meant that it was not feasible to conduct a systematic review of all potential topics. It was decided to create a list of research questions representing those clinical topics based on the information gathered from assessment of MMT physicians where there was believed to be the greatest variation in practice and/or divergence of clinical opinion. To determine the research questions, a survey was developed to poll Methadone Assessors, Methadone Committee and the Patient Advisory Group. Results of the survey were analyzed to determine the strongest trends, as well as having a balance between patient/public safety and patient retention. With the assistance of the Research Advisory Group, these were translated into questions suitable for a focused literature search. These questions included:

1. What is the impact of concurrent use of benzodiazepines on patient mortality?
2. How effective is methadone maintenance therapy (MMT)[1] in the treatment of addiction to prescription opioids?
3. What is the impact of the frequency of urine drug screening on patient retention?
4. What is the relative effectiveness of point-of-care versus chromatography urine drug screening?
5. What is the impact of methadone tapering on relapse or abstinence?
6. What is the effectiveness of medical detoxification?
7. How effective are take-home doses in achieving optimal MMT outcomes?
8. What is the effectiveness of MMT for special populations[2]?
9. How is clinical stability determined?

[1] MMT effectiveness defined as: patient retention and other outcomes

[2] Special populations defined as: pregnant patients; older people; younger people; psychiatric co-morbidity; cardiac conditions

1.4.2 Literature Search Methods:

A search for English language publications, 2000s onwards was conducted on databases:

- Medline (National Library of Medicine)
- Embase: Exerpta Medica
- PsychINFO (American Psychological Association)
- Scopus and others (recent literature)
- Cochrane Database of Systematic Reviews

Search strategies were database specific, based on the subject headings used to index these databases. Subject Heading search terms were combined with appropriate keywords. For databases not indexed with subject headings, such as Scopus and In Process Medline, only key word searches were conducted.

Grey Literature was also searched by: 1) targeting the websites of key organizations throughout the world for guidelines, evaluations and policy documents; and 2) searching library catalogues, such as the CAMH Library catalogue and 3) other MMT guidelines.

1.4.3 Rating Quality of Evidence

An adaptation of the Harbour and Miller (2001) system for grading recommendations in evidence based guidelines was used to grade evidence quality. Levels of evidence are based on study design and methodological quality of individual studies.

Hierarchy of Study Design	Strength of Evidence
I Systematic Reviews & Meta-analysis of Controlled Trials	Strong
II Randomized Control Trials	Strong
III Non- randomized intervention studies (pre-post study design; matched controls; time series)	Moderate
IV Observational studies (cohort studies; cross sectional, retrospective study designs)	Low
V Non-experimental designs (case reports; qualitative research)	Very low
VI Expert Opinion; reports of Expert Committees	Very low

1.4.4 Summary of Evidence Synthesis Key Findings

Question 1:
What is the impact of concurrent use of benzodiazepines on patient mortality?

- 32 articles were identified and 7 were excluded (5 not published in English and 2 unrelated to the topic)
- Studies investigating the use of benzodiazepines in MMT patients are for the most part observational and therefore the quality of evidence is low (Level IV).
- BZD use is associated with a variety of adverse consequences, such as increased psychological distress, risk for overdose, higher risk of suicidal behaviour, impaired attention and memory (Bleich et al. 2002: Brands et al. 2008; Caplehorn and Drummer, 2002; Darke etal. 2010; Darke et al 2009; Demaria et al. 200; Man Lan-Ho et al., 2004).

Question 2:
How effective is MMT in the treatment of addiction to prescription opioids?

- 4 studies that were relevant to this question were identified, all providing a low level of evidence (Level IV – Level VI).
    - Prescription opioid users can be treated at least as effectively as heroin users in MMT (Banta-Green et al. 2009).
    - Prescription-opioid users often have pain problems and obtain their opioids legally from a prescriber indicating that they were still under medical supervision for their pain; these patients were more likely to have psychiatric treatment and take sedatives/anxiolytics or anti-depressants (Brands et al. 2004)
- National Institute on Drug Abuse Clinical Trials Network launched the Prescription Opioid Addiction Treatment Study (POATS) to address the increasing rates of prescription opioid addiction. The study is taking place at 10 community treatment programs around the United States. Men and women age of 18 years or older will receive buprenorphine/naloxone. The results of this study should provide further understanding of the treatment of prescription opioid addiction (Weiss et al., 2010).

Question 3 and 4:
What is the impact of urine drug screening on patient retention?

- Only 8 studies were identified as relevant or somewhat relevant to the impact of urine drug screening on patient retention in MMT.
- One RCT showed that methadone take-home doses contingent on a minimum of monthly drug-free urines prevents declines in treatment outcomes; better results were achieved by weekly-urine testing (Chutuape et al. 2001).

Question 5:
What is the impact of methadone tapering on relapse or abstinence?

- Some of the studies that were reviewed overlapped somewhat with the studies that were related to the use of methadone for detoxification (research question #6).
- 3 studies were identified as being relevant to the impact of tapering on effectiveness of MMT: 1 systematic review, 1 RCT (moderate level of evidence due to small sample size), 1 observational study (low level of evidence)
- Systematic Review (somewhat relevant) evaluated the effectiveness of methadone tapers compared to *Levo-Alpha Acetyl Methadol* (LAAM), buprenorphine and clonidine in managing opioid withdrawal and on completion of detoxification. Overall methadone tapers were as effective as other pharmacological agents used for detoxification from opioids (Amato et al. 2004).

Question 6:
What is the effectiveness of methadone for medical detoxification?

- 22 studies identified as being relevant or somewhat relevant to the topic, of which 10 provided very low evidence on the utilization of methadone for detoxification from opioids (Level IV-V).
- 1 systematic review found that the overall effectiveness of a methadone taper was similar to other pharmacological agents (buprenorphine, LAAM, adrenergic agonists) used for detoxification from opioids (Amato et al. 2004).
- Another systematic review of the outcomes of planned detoxification from methadone found high relapse rates among those who completed therapeutically planned methadone tapers, particularly during the first year after the completed tapers (Magura and Rosenblum 2001).

Question 7:
How effective are take-home doses in achieving optimal MMT outcomes?

- 11 articles were identified as being relevant or somewhat relevant to the research question; they addressed various aspects of take-home dose regimes, such as criteria for take-home doses, safety issues and diversion, urine testing and take-home schedules.
- 9 articles were excluded (8 not relevant to the research question and 1 not published in English)
- Strong evidence that methadone take-home doses contingent on drug-free urines prevent decline in treatment outcomes (one study) (Chutuape et al., 2001).

Question 8:
What is the effectiveness of MMT for special populations?

- Pregnancy: strong evidence showing that MMT provides greater social stabilization and prenatal care (Binder and Vavrinkova 2008).
- HIV/HCV: strong evidence for beneficial effect of MMT on HIV risk behaviours and decreased mortality from overdoses (Farrell et al., 2005)
- Youth: 6 studies (low level of evidence)
  - One trial in the US compared 12 weeks of buprenorphine/naloxone to 14 day teper in opioid-dependent youth (6 community out-patient treatment programs). The authors found that continued buprenorphine treatment is more cost effective compared to brief detoxification (Polsky et al. 2010).
- Psychiatric Disorders: 43 studies relevant or somewhat relevant, more than half were of low or very low quality
  - Depressed patients can be more sensitive to opioid withdrawal (Astalset al. 2008; Cacciola et al. 2001; Callaly et al. 2001; Deyer et al. 2005; Elkader et al. 2009; McManus et al. 2007)

Question 9:
How is clinical stability determined?

- Various factors were identified as having an impact on clinical stability, such as treatment retention (15 studies); methadone dose (7 studies), other drug use (8), and impact of counselling and psychotherapy (4 studies).
  - Strong evidence (Level I) on the positive effects of MMT on retention, reduction of illicit opioid use and criminality (Johansson et al. 2007)
  - Meta-analysis (Strong evidence, Level I) reported that higher doses of methadone and individualization of doses are associated with better retention in MMT (Bao et al. 2009).
- Many studies and guidelines cite criteria for clinical stability originally published in the US Federal Register, vol. 66, no 11, Wednesday, Jan 17, 2001 (SAMSHA).

2. Introduction

2.1 History of MMT in the Treatment of Opioid Dependence

In the early 1900s in the United States, opioid dependence was treated in physicians' offices with morphine. However, as the social issues associated with opioid dependence became increasingly apparent, the government of the day initiated behavioural treatment approaches at "narcotics farms" and other hospital-like settings that confined and committed addicts to abstinence and

presumed recovery. Many of these programs proved costly and ineffective with high post-discharge relapse rates. Pharmacotherapy was a missing component.

During the Second World War, methadone, a long-acting pure mμ agonist, was developed by Bayer in Germany as an analgesic. It was considered to be a non-addictive alternative to morphine. In the 1940s, several studies conducted in the United Kingdom recognized methadone as an efficacious treatment of heroin withdrawal symptoms. In the 1950s and 60s, as opioid use became a serious concern in urban areas with resultant dramatic increases in crime and death rates, researchers and physicians became involved in trying to find a medical solution to opioid dependence. In late 1963 and early1964, the first methadone study was performed at The Rockefeller Institute for Medical Research by Drs. Dole and Nyswander in an attempt to develop a new pharmacotherapy for opiate dependence (Dole and Nyswander 1965; Dole and Nyswander 1966). Their research concluded that methadone prevented opioid withdrawal symptoms, blocked the euphoria of heroin, and decreased cravings in opioid-dependent individuals and thereby confirmed methadone efficacious as a maintenance medication for opioid dependence.

Meanwhile, it was actually a Canadian researcher, Dr. Robert Halliday from Vancouver, who set up what is believed to be the first MMT program in the world. Since that time, opioid agonist therapy with MMT has become an effective treatment option for opioid-dependent individuals worldwide. In many countries, including Canada, more people are seeking and receiving treatment with MMT.

In Canada, it is estimated that there are more than 80,000 regular illicit opioid users, 30,000 in Ontario (Popova et al. 2006**).** The multisite OPICAN study, with a cohort of regular untreated illicit opioid users from seven Canadian cities surveyed from 2001 until 2005, provides evidence suggesting that heroin has become an increasingly marginal form of drug use among illicit opioid users in Canada, and that instead, prescription opioids in varying forms have become the predominant form of illicit opioid use (Fisher et al. 2005)**.** A chart review of new admissions (1997-1999) to the MMT program at the Centre for Addiction and Mental Health (CAMH) revealed that 83% of patients had used prescription opioids ± heroin (Brands et al. 2004)**.** Also, between 1990 and 1994, there was a significant rise in individuals addicted to controlled-release oxycodone seeking treatment at CAMH (Sproule et al. 2009). The semi-synthetic oxycodone and full synthetic fentanyl have been linked to several deaths in Ontario (Dhalla 2009, Martin et al. 2006)**.**

Literature on the effectiveness of MMT in the treatment of prescription opioid addiction is sparse. Banta-Green, et al.reported that prescription opioid users can be treated at least as effectively as heroin users in MMT (Banta-Green et al. 2009). Prescription-opioid users often have pain problems and obtain their opioids legally from a prescriber indicating that they were still under medical supervision for their pain; these patients were more likely to have psychiatric treatment and take sedatives/anxiolytics or antidepressants (Brands et al. 2004).

MMT is based on a harm reduction philosophy and represents one component of a continuum of treatment approaches for opioid-dependent individuals. MMT is a substitution therapy that allows a return-to-normal physiological, psychological and societal functioning. It is one possible treatment for opioid dependence. For some people, MMT may continue for life, while others may be able to eventually discontinue MMT and remain abstinent while preserving the normal level of function they attained while on MMT. Each patient must be assessed, treated,

and monitored on an individual basis. Successful outcomes through MMT require knowledge, experience, vigilance, and diligence on the part of the MMT physician, the patient, and all of those involved in treatment.
Methadone alone does not constitute effective treatment of opioid dependency. Effective MMT services should comprise the following components:

- an appropriate methadone dose
- routine medical care
- treatment for other substance dependence
- counselling and support
- mental health services
- health promotion, disease prevention and education
- linkages to other community-based services
- outreach and advocacy.

2.2 Effectiveness of Methadone

Methadone has been extensively researched for safety and its efficacy to reduce morbidity and mortality in opioid dependent patients. The research data and medical literature shows that:

- MMT reduces morbidity and mortality associated with heroin addiction (Gunne and Gronbladh 1981; Kinlock et al. 2009; Newman and Whitehill 1979; Strain et al. 1993).One study found that patients were three times as likely to die without MMT than if they were maintained on treatment (Caplehorn et al. 1994). In addition, studies have shown that MMT can indirectly decrease mortality by decreasing the risk of HIV infection while on MMT (Ball et al. 1988; Caplehorn and Ross 1995). A Cochrane review (Mattick et al. 2009) of 11 randomized clinical trials found that methadone was more effective than non-pharmacological treatments with respect to the outcomes of treatment retention and suppression of heroin use. The great majority of trials were with heroin users.
- There is evidence that MMT reduces illicit opioid and other drug use (Gunne and Gronbladh 1981; Kinlock et al. 2009; Yancovitz et al. 1991). For example, an early trial found that compared to methadone, the control group was more than three times likely to test positive for heroin use at a one-month follow-up after treatment (Yancovitz et al. 1991). MMT also reduces other substance use. One large prospective study (Fairbank et al. 1993) of methadone patients found a reduction in the use of cocaine, amphetamines, illegal methadone, sedatives, and marijuana at follow-up. Other factors associated with decreased drug use include counselling, adequate dosing, contingency management strategies such as take-home doses, and harm reduction program orientation (Kletter 2003; Kraft et al. 1997; Ling et al. 1996; McLellan et al. 1993; Stitzer et al. 1992; Villano et al. 2002).
- There remain few studies on the effectiveness of MMT for prescription opioid (PO) abuse and dependence.
- Methadone is a = receptor agonist with pharmacological properties similar to those of morphine. It exists as two isomers (d and 1 forms) but it is believed that most of the analgesic activity resides in the 1 isomer (Scott et al. 1948). However, most of the methadone used in clinics is a racemic mixture. Methadone has ideal properties for a

maintenance agent: it is orally active and long-acting (one dose suppresses symptoms of opoid withdrawal for 24-36 hours without producing euphoria, sedation and analgesia). This enables patients to function normally (i.e, without impairment) and experience normal pain and emotional responses. Another advantage of methadone is the ability to suppress craving (Lowinson et al. 2005).

Methadone is well absorbed after oral administration and levels are detectable at 30 minutes with peak concentrations occurring at 4 hours and it is 90% bound to plasma proteins. Methadone is extensively metabolized in the liver to pyrrolidines and pyrroline (via *N*-demethylation and cyclization) which are then excreted in urine and bile (Gutstein and Akil, 2006). The elimination half-life ($t_{1/2}$) of methadone is approximately 22 hours but there is considerable inter-indivdual variability and estimates range from 5-130 hours (Eap et al. 2002).

2.3 Professional Duties

MMT physicians are responsible for the following:

1. Provide professional, respectful and reliable services to patients
2. Provide back-up coverage for periods when on vacation or otherwise unavailable
3. Provide appropriate notice should they close their MMT practice
4. Assist in the transfer of patients to other MMT physicians
5. Provide or facilitate patient access to health and social services, such as counselling and primary health care
6. Remain current in practices and standards for MMT and the treatment of opioid dependence
7. Communicating and collaborating with pharmacists and other care providers for the benefit of the patient.

2.4 Interprofessional Collaboration (IPC)

2.4.1 Physician-Pharmacist Collaboration and Communication

Many problems in patient care have been found to be a direct result of lack of communication between MMT prescriber and pharmacist (CAMH, November 24th, 2010). To optimize patient care, communication between physicians and pharmacists is essential in the following:

- Determining at the outset of treatment whether a pharmacy is accepting new patients
- Discussing how and when the pharmacist is to contact the MMT prescriber
- Developing means for the pharmacist to reach the MMT prescriber for urgent issues after hours
- Documenting or relaying pertinent clinical information (e.g. pregnancy), missed doses, vomited doses.

Interprofessional collaboration is a principle supported by both CPSO and OCP. The pharmacist and the physician play an important role in MMT. This can include joint development of policies and procedures to ensure continuity of patient care and secure custody and storage of methadone. Collaboration and regular communication between

pharmacists and MMT prescribers can have positive impact on patient care and safety (OCP, September 2010).

2.4.2 Physician-Patient-Pharmacist 3-Way Treatment Agreements

In order to facilitate collaborative communication, 3-way agreements between the physician-patient-pharmacist are encouraged. These 3-way agreements are similar to current Treatment Agreements between the physician and the patient but include the pharmacist as well. (See Appendix G Sample Physician/Pharmacist/Patient Agreement Letter) The patient should always be given the opportunity to select their choice of pharmacy. Additionally, beyond the 3-way treatment agreements, a pharmacy will also have a Patient-Pharmacist Agreement (CAMH, 2004) to cover procedural issues specific to the pharmacy.

2.5 Conclusion

The medical literature supports that MMT is a well established and cost-effective treatment paradigm. MMT saves lives and reduces violent and non-violent crime; drug use; and the transmission of HIV, Hepatitis C, and other communicable diseases. The effectiveness of MMT is enhanced with contingency management and counselling.

3. MMT Physicians and Practice Settings

3.1 Overview

MMT is prescribed in different settings, using different models of care such as: primary care, MMT focused practices, community-based agencies, hospitals, chemical withdrawal units (CWU), residential addiction treatment centres, and correctional facilities. This section outlines the requirements of all MMT prescribers in these practice settings.

▶ Standard

S3.1	As of January 1, 2009, the MMT physician shall complete: 1) the Opioid Dependence Treatment Core Course prior to obtaining a methadone exemption, **and** 2) the full Opioid Dependence Certificate Program within 3 years of receiving an exemption.

3.2 Obtaining a Methadone Exemption

For an exemption to prescribe MMT, a physician must:

- Hold a certificate of registration in Ontario
- Be in good standing with the CPSO
- Complete an application form and agree to practice in accordance with the CPSO's expectation document (available at CPSO)
- Complete the Opioid Dependence Treatment Core Course through CAMH
- Complete two days of clinical training with a MMT physician approved by the CPSO.

The initial exemption is issued for one year with subsequent exemptions issued every three years. For more information contact the CPSO Methadone Program (416) 967-2661.

3.3 MMT Physician Practice Settings

3.3.1 Primary Care MMT Practice

General practitioners and family physicians may provide MMT in solo medical practice or group practices such as Family Health Teams, private medical clinics, hospital-based health clinics and community-based health centers, including chronic care centers. They may prescribe methadone either integrated with or separate from their medical practice. Some MMT patients in Ontario receive medical care as well as MMT from their primary-care physician. Some physicians in private practice provide psychotherapy as well as MMT and other medical services.

MMT based in primary practice has several advantages, such as being less stigmatizing and addressing previously unmet medical needs (Fiellin et al. 2001; King et al. 2002; Lewis and Bellis 2001; Merrill et al. 2005). However, patients may have to travel to receive pharmacy, laboratory, and other specialized addiction and support services. Group practices may have advantages over solo practice. Research by Strike et al. (2005) indicates that group practices

may have better retention rates than solo practitioners and the integration of primary-care services within group practices is likely to lead to better outcomes for MMT patients.

3.3.2 MMT-Focused Practice

MMT physicians who work in focused methadone clinics (both outpatient and inpatient) may be general practitioners, family physicians, or Royal College of Physicians and Surgeons Specialists. Such physicians have additional training or exam certification in Addiction Medicine and focus their clinical practices in MMT; their practices may consist entirely or predominantly of MMT patients. Many MMT patients in Ontario receive their care in this model.

MMT physicians in focused practices generally do not provide primary care to their patients. Patients may need to seek out primary care or psychosocial services in the community.

3.3.3 Community-Based MMT Practice

Community-based physicians may provide services through publicly-funded, community based clinics that integrate psycho-social care. Examples include HIV/AIDS services, mental health agencies, and clinics run by local public health departments. These clinics often specialize in serving specific populations or issues such as HIV/AIDS, Hep.C, marginalized, street-involved, or homeless populations. Many community-based clinics operate under a harm-reduction philosophy and involve a multi-disciplinary team (social workers, nurses, case managers, dieticians, pharmacists) in the patient's care.

These clinics usually offer a comprehensive MMT program that includes health and social supports. This kind of one-stop clinic model saves time and expenses for the patient and addresses the patients' quality of life issues. It also helps ensure better coordination and communication among the service providers.

3.3.4 Hospital and Corrections-Based MMT Practice

MMT physicians in hospitals and some residential addiction-treatment centres maintain patients on their community-based MMT program or may initiate MMT in some circumstances.

Hospital-based physicians providing care for MMT patients may apply for temporary methadone exemptions, one patient at a time, to manage admitted medical, surgical, and psychiatric patients. They may not have specialized knowledge of opioid dependence (see Section 15 Hospital-Based MMT).

Correctional facilities manage many patients with opioid dependence and may provide MMT (see Section 14: MMT in Federal/Provincial Correctional Facilities).

4. Pharmacotherapy Options other than MMT for Opioid Dependence

4.1 Overview

The main treatment options for opioid dependence are abstinence based treatments and opioid agonist therapy (also known as opioid substitution therapy) with methadone or buprenorphine. MMT physicians must be familiar with the indications, benefits, and risks of each option, in order to provide the safest and most effective treatment for their patients.

►Standards

S4.1	The MMT physician shall inform the patient of all the treatment options to treat opioid dependence, including risks and benefits, so they may make an informed decision about the use of MMT prior to initiation.
S4.2	Physicians who prescribe buprenorphine shall have the appropriate knowledge, skills, and judgment to do so.

►Guideline

G4.1	The MMT physician should be familiar with the individual patient factors to be taken into consideration in the choice for buprenorphine as an opioid agonist therapy.

4.2 Abstinence Based Treatments

Abstinence based treatment may consist of medically supervised withdrawal from opioids, followed by an inpatient or outpatient psychosocial treatment program, and/or 12 Step group participation (AA, CA, NA). While abstinence based treatment is less effective than MMT, patients may prefer a trial of abstinence before committing to long-term opioid agonist therapy (Richman et al. 1972).

Patients should be warned that after detoxification 1) as a result of losing their tolerance to opioids, they are at risk for overdose if they relapse to their usual opioid dose, and 2) emotional distress associated with opioid withdrawal may increase the risk of suicidal ideation. MMT physicians should take appropriate precautions to avoid these adverse outcomes.

Patients may choose naltrexone treatment after detoxification from opioids. Naltrexone, a long-acting opioid antagonist, may be prescribed to patients as a deterrent to opioid use. The MMT physician should be fully aware of the management issues for naltrexone treatment for opioid dependence prior to initiating such therapy.

4.2.1 Indications for Abstinence Based Treatment

Patient preference. Many patients prefer a trial of detoxification first, as some view opioid agonist treatment as inconvenient and time consuming.

Prior sustained response to abstinence based treatment. Patients may consider re-trying abstinence based treatment if they previously maintained a long period of abstinence following psychosocial treatment.

Good prognostic factors. Patients may be more prepared for medically supported withdrawal followed by abstinence if they are highly motivated for change and opioid abstinence, and have good prognostic factors for recovery from addiction. (e.g., socially stable, supportive social network, short duration of addiction, no major psychiatric co-morbidity, not addicted to other drugs) (Gossop et al. 1989; 1990; Rabinowitz et al. 1997; Unnithan et al. 1992; Washton et al. 1984).

4.2.2 Pharmacotherapy for the Systematic Treatment of Opioid Withdrawal

The most common drugs used to alleviate opioid withdrawal symptoms are alpha adrenergic agonist (e.g., clonidine), and opioid agonists (e.g., methadone and buprenorphine). See Table 01.

Table 01: Withdrawal Management

Drug	Dose	Opioid Withdrawal Symptoms
Clonidine	0.1 mg 1–2 tabs p.o. b.i.d.to q.i.d. p.r.n.	agitation, diaphoresis, and sympathetic overdrive
Dimenhydrinate	50 mg p.o. or p.r. p.r.n.	nausea
Ibuprofen	200 mg 1–2 tabs p.o. t.i.d. p.r.n.	myalgia
Immodium	2 mg p.o. p.r.n. (maximum 6 tabs/day)	diarrhea stool
Trazodone	50–100 mg p.o. q.h.s. p.r.n.	insomnia
Benzodiazepines	p.r.n. at MMT physician's discretion	anxiety

4.3 Opioid Agonist Treatment

Long-acting opioids used in the treatment of opioid dependence include buprenorphine and methadone. This section discusses the use of buprenorphine.

4.3.1 Buprenorphine

Buprenorphine-naloxone (Suboxone®) is a sublingual partial mμ agonist that, at the appropriate dose, relieves withdrawal symptoms and cravings for 24 hours or more. Because it has a ceiling effect, buprenorphine appears to be safer in overdose compared to methadone (Mattick et al. 2008; Veilleux et al. 2010). However, buprenorphine may also be somewhat less effective than methadone at retaining patients in treatment (Mattick et al 2008). The maximum dose for buprenorphine (24 mg) is probably less effective than methadone at doses above 60 or 80 mg, and thus, methadone may be more appropriate for patients who are dependent on large doses of opioids. Patients who have failed at buprenorphine treatment may be switched to MMT; switching from methadone to buprenorphine is clinically more difficult (Greenwald et al. 2003; Levin et al. 1997; Petitjean et al. 2001).

Buprenorphine is very unlikely to replace MMT, and the two medications should be viewed as complementary. Until further research is available, the choice between MMT or buprenorphine should be based on individual patient factors and patient preference.

4.3.2 Indications for Buprenorphine Treatment

While there is a lack of definitive evidence on the indications for choosing buprenorphine over methadone, MMT physicians may want to consider prescribing buprenorphine in the following particular patient groups:

- Patients with prolonged QTc interval secondary to methadone treatment or any other cause (Fanoe et al. 2007; Wedam et al. 2007).
- Patients at higher risk for methadone toxicity: Elderly patients, those taking benzodiazepines (Schottenfeld 1988) or other sedating drugs, with heavy alcohol consumption, COPD or other respiratory illness, and patients with lower tolerance to opioids (e.g., on codeine, or less than daily opioid use) (Corkery et al. 2004; Mikolaenko et al. 2002; Pergolizzi et al. 2008).
- Adolescent and young adult patients. Recent literature reports that buprenorphine with behavioural interventions is significantly more efficacious in the treatment of opioid-dependent adolescents compared to clonidine plus behavioural intervention (Marsch et al. 2005).
- Patients with good prognosis who may be able to successfully taper off opioid agonist treatment after 6-12 months. The literature indicates that buprenorphine has a milder withdrawal syndrome and may be easier to discontinue than methadone (Woody et al. 2008).
- Patients for whom methadone take-home restrictions may cause them to drop out of treatment because of lack of transportation or work or family commitments.
- Patients for whom methadone take-home restrictions may not be as necessary because they are at lower risk for overdose, misuse and diversion (e.g., they take prescription opioids orally from only one physician, are not abusing street drugs, and are not selling or buying their opioids).

4.3.3 Buprenorphine: Practical Issues

- In Canada, buprenorphine is available as Suboxone®, a buprenorphine/naloxone combination product.
- As with other opioids, buprenorphine is subject to federal Controlled Drugs and Substances Act.
- Patients will not be registered with the CPSO.
- Physicians do not need special authorization to prescribe; the CPSO expects physicians who prescribe buprenorphine to have the appropriate knowledge, skills and judgment to do so.

Guidelines for the provision of buprenorphine are under development at the Centre for Addiction and Mental Health (CAMH). The Guideline will provide recommendations on take-home dosing, urine drug screening (UDS) and other clinical practices. For any further information about training in buprenorphine prescribing, contact CAMH at (416) 535-8501 or www.camh.net.

4.4 Conclusion

Table 02: Consideration of Factors for Buprenorphine vs Methadone vs Abstinence-based Treatment

Abstinence-based treatment	Buprenorphine	Methadone
• Patient preference • Good prognostic factors • Has not tried abstinence-based treatment • Had a prolonged period of abstinence following previous abstinence-based treatment	• Failed or had adverse effects with methadone • Quickly relapsed after withdrawal management • Good prognosis; may not need long-term opioid agonist treatment • At higher risk for methadone toxicity	• Failed or had adverse effects with buprenorphine • Quickly relapsed after withdrawal management • Intravenous buprenorphine abuse • High risk for treatment drop-out

5. Initial Patient Assessment

5.1 Overview

Initial patient assessment for MMT involves assessing for suitability for MMT, a history and brief physical examination, urine drug screening and other investigations, and a discussion and review of treatment options and necessary documents pertinent to MMT.

►Standards

S5.1	The MMT physician shall establish that the patient meets the DSM IV criteria for opioid dependence prior to MMT initiation (see Appendix A).
S5.2	The MMT physician shall be knowledgeable of any potential risks for methadone toxicity prior to MMT initiation and manage the patient's care appropriately.
S5.3	The MMT physician shall register patients with the CPSO.

►Guidelines

G5.1	The MMT physician should consider abstinence based treatment and/or opioid substitution for withdrawal purposes for patient's under18 years of age with a shorter duration of opioid dependence.
G5.2	The MMT physician should consider MMT for patients under 18 years of age only after a thorough assessment and discussion about all treatment options.
G5.3	The MMT physician should ensure there has been a discussion with patients under 18 years of age (and other family members where possible) about potential issues with methadone including side effects, risks and difficulty withdrawing and tapering off of methadone.
G5.4	The MMT physician should seek and document consultations, formal or informal, with a methadone provider prior to initiating a patient under 18 years of age on MMT.
G5.5	For all patients that may be initiated on MMT, the physician should document the following in addition to a medical history: 1) pattern of use of all major drug classes (including tobacco and alcohol) 2) addiction treatment history and response 3) high-risk behaviour, such as needle sharing and sex trading 4) psychiatric history, current mental status (particularly suicidal ideation) 5) social situation (including child custody and the partner's drug use history) 6) details regarding chronic or recurrent pain.
G5.6	The MMT physician should conduct a focused physical examination prior to initiating MMT or within a reasonable amount of time (i.e. during the early stabilization phase)
G5.7	If an initial UDS for methadone is positive, the MMT physician should confirm that the patient is not on another MMT program by receiving approval from the CPSO prior to initiating MMT.
G5.8	The MMT physician should request bloodwork which includes HIV, and hepatitis B and C serology during initiation or within a reasonable amount of time after initiation on MMT.
G5.9	The MMT physician should test for pregnancy in female patients of childbearing potential prior to initiating MMT.
G5.10	The MMT physician may initiate MMT prior to receiving confirmation from CPSO if the initial UDS is not positive for methadone or EDDP.
G5.11	The MMT physician should have a written Treatment Agreement signed by the patient and documented in the chart. See Appendix D MMT Agreement

5.2 Suggested Criteria for MMT

The MMT physician should consider the suggested criteria for MMT prior to initiation:

1. Opioid use (a urine drug screen that is positive for opioids and verifies the patient's history).
2. Meets DSM IV criteria for opioid dependence.
3. Lower likelihood of benefit from non- MMT treatments.
4. Agreement to terms and conditions of the MMT program.

Patients may be suitable candidates for MMT even if it was unsuccessful or discontinued in the past.

5.2.1 Adolescents

Patients under 18 years of age may be considered for MMT, however abstinence based treatment and/or opioid substitution tapering should also be considered for adolescents, particularly those with a shorter duration of opioid dependence. Any treatment option involving withdrawal should be avoided if the patient is pregnant. Methadone should be considered after a thorough assessment and a discussion about all treatment options has taken place. The MMT physician should ensure that there has been a discussion with the adolescent (and other family members where possible) about potential issues with methadone including side effects, risks and difficulty of tapering off.

In cases where a MMT physician considers it appropriate to offer an adolescent MMT, it is recommended that the MMT physician consider seeking assistance by referral and may request a consultation (formal or informal) with another MMT physician.

Currently, there is a lack of evidence on the effectiveness of MMT in adolescents. However, several studies in the United States are investigating the use of buprenorphine-naloxone in opioid dependent youth (Chakrabarti et al.; Polsky et al. 2010; Subramaniam et al. 2009).

5.3 Assessing a Patient for MMT Initiation

See Appendix E for Patient Initiation to MMT Form.

5.3.1 Patient History

There are a number of important areas to concentrate on with regards to patient history for this population of patients. See Appendix C Initial Patient Assessment Form

1. Ensure the patient meets the DSM IV criteria for opioid dependence prior to MMT initiation.
2. Identify any potential risks for methadone toxicity prior to MMT initiation (see Table 03)
3. Pattern of use of all major drug classes (including tobacco and alcohol).
4. Previous addiction treatment history and response.
5. High risk behaviour such as needle sharing and sex trading.
6. Psychiatric history and current mental status including suicidal ideation.
7. Social situation including housing, supports, child custody, and partners drug-use history.
8. Details regarding chronic or recurrent pain.

Table 03: Patient Factors that Increase Risk of Methadone Toxicity

High Risk Patients
Recent benzodiazepine use
Use of other sedating drugs
Alcohol-dependent patients
Over 60 years old
Respiratory Illnesses
Taking drugs that inhibit methadone metabolism
Lower opioid tolerance
Decompensated hepatic disease
Recent discharge from inpatient rehabilitation facility
Recent incarceration

5.3.2 Elderly

One study showed that older adult MMT patients (> 55 years old) were more likely to report alcohol use and in general, their quality of life did not improve with aging and length of tenure in MMT (Rajaratnam et al. 2009). Firoz and Carlson did not find any differences between MMT patients older than 55 years and their younger counterparts in terms of medical, psychiatric or employment problems (Firoz and Carlson 2004). Schroeder et al provided strong evidence on the significantly higher rates of adverse events (infections, gastrointestinal, musculoskeletal) among female MMT patients, while participants over age 40 reported lower rates of adverse events (Schroeder et al. 2005). Tuchman reported that close correspondence of menopausal symptoms and opiate withdrawal/methadone symptoms can result in inadequate medical attention to problems related to methadone maintenance (Tuchman 2007; 2010).

5.3.3 Focused Physical Examination

The MMT physician should conduct a focused physical examination prior to initiating MMT or within a reasonable amount of time (i.e., during the early stabilization phase). Special attention should be given to signs of opioid withdrawal, malnutrition, jaundice, hepatosplenomegaly, cardiovascular and respiratory status, pupil size, needle tracks, and abscesses.

5.3.4. Urine Drug Screening (UDS)

Initial urine drug screening facilitates objective corroboration of the patient history of opioid drug use. Some particular UDS results need to be taken into consideration prior to MMT initiation.

5.3.4.1 Initial Opioid Positive Urine without Differentiating/Identifying the Specific Opioid

A patient may be appropriate for initiation on methadone even if their initial urine drug screen is positive for opioids, but does not identify the specific opioid that the patient has reported as their opioid of abuse, if the following circumstances are met:

1. the patient has signs and symptoms of obvious opioid withdrawal **OR**
2. the patient has obvious track marks **OR**
3. the patient has been on previous MMT **OR**
4. the physician has corroborating information from a previous opioid prescribing physician.

5.3.4.2 Methadone-Positive Initial UDS

There are many patients who come for an initial assessment for MMT who have previously tried/used methadone that was not prescribed for them. With a positive initial UDS for methadone or EDDP (a methadone metabolite), it is important to document the patient's history of methadone use. To avoid MMT duplication and toxicity, the MMT physician should also contact the CPSO to ensure that the patient is not on another MMT program and receive confirmation from the CPSO prior to initiating the patient on methadone.

5.3.5 Other Tests

In addition to UDS, the MMT physician should request bloodwork for HIV, Hepatitis B and C serology and any other relevant bloodwork during initiation or within a reasonable amount of time after initiation on MMT. Occasionally, patients refuse or will not comply with this directive. The MMT physician should discuss the concerns with the patient and document the discussion.

In females of childbearing potential, a urine pregnancy test should be done prior to initiating MMT.

5.4 MMT Program Documentation

5.4.1 CPSO Registration

Patients may not receive a prescription for methadone from more than one source at a time. For this reason, prior to initiating treatment, the MMT physician should register patients for treatment with the CPSO to ensure the patient does not receive treatment elsewhere. A clinical decision may be made to start MMT before receiving CPSO approval if there is a concern that a delay in initiation will cause the patient undue harm or cause the patient to drop out of treatment. (See Appendix E Patient Initiation to MMT Form) The MMT physician should await approval from the CPSO in the case of EDDP/methadone positive initial urine drug screen.

5.4.2. Treatment Agreement

Written Treatment Agreements, or Letters of Understanding, are documents that list expectations of involvement in a MMT program. The use of treatment agreements in MMT programs has proven beneficial to both the patient and the MMT physician. A signed Treatment Agreement is documentation of informed consent. (See Appendix D: Sample Methadone Maintenance Treatment Agreement).

Treatment Agreement should include:

- Patient and provider roles and responsibilities
- MMT program expectations and structure
- Doctor patient confidentiality and exceptions to this
- Expectations of communication with other appropriate providers (pharmacist, treating primary care physicians and consultants)
- General consent (e.g., access to patient charts for MMT physician assessment of their MMT practice).

It is recommended that the MMT physician communicate his/her expectations with the pharmacist at pharmacies where their patient's methadone is dispensed. This can be accomplished through one of the following:

1. Three way treatment agreement between the patient, the MMT physician and the pharmacist.
2. Letter to the pharmacist outlining details of your treatment agreement with your patient along with your expectations regarding missed doses, intoxication. This may also include your contact information in case of emergency. (See Appendix G: Sample Physician/Pharmacist/Patient Agreement Letter).
3. Verbal discussion with the pharmacist outlining the details of the MMT physician treatment agreement with the MMT patient along with the MMT physician's expectations regarding missed doses, intoxication. It may also include communicating the MMT physician contact information in case of emergency.

6. Dosing During Initiation, Stabilization and Maintenance

6.1 Overview

Patients are at a high risk of death from methadone overdose in the first two weeks of MMT**.** Recent prospective population studies from the UK and Australia have revealed that during the first two weeks of methadone treatment the crude mortality rate was 17 per 1000 person years (Cornish et al. 2010; Degenhardt et al. 2009). The risk of fatal methadone overdose during this time period is estimated to be 6.7 times higher than that of heroin addicts not in treatment, and 98 times higher than that of patients on maintenance doses of methadone in treatment for longer periods (Caplehorn and Drummer 1999). A single day's MMT dose can be lethal to non-tolerant individuals. (Harding-Pink, D 1993)**.** The ratio between the maximum recommended initial dose (30 mg) and a potentially fatal single dose is exceedingly narrow compared to other medications (Repchinsky 2003; Wolff 2002)**.**

The prolonged half life (as long as 55 hours in methadone naïve individuals) and slow bioaccumulation of methadone accounts for its insidious onset of overdose. During dose increases, serum levels accumulate over several days even if the dose is kept the same. Therefore, a dose that is barely adequate on day one can be toxic by day 3-5. This is particularily relevant during initiation on MMT. The patient may appear relatively alert during the day succumbing to an overdose during a nap or at night. Early signs of toxicity include ataxia, slurred speech, "nodding off," and emotional lability (Caplehorn and Drummer 2002).

Concurrent use of benzodiazepines, alcohol, and other sedating drugs substantially increases the risk of death from methadone toxicity. One study found evidence of polydrug use in 92% of methadone-related deaths (Zador and Sunjic 2000). Animal studies indicate that benzodiazepine use substantially increases the risk of fatal overdose (Caplehorn, JR and Drummer, OH, 2002.)

►Standards

S6.1	On the methadone prescription, the MMT physician shall specifiy: 1) Start and end dates 2) Days of week that are to be supervised 3) Number of take-home doses and days of week that are to be given as take-home doses 4) The dose written in numbers and words.
S6.2	The MMT physician shall counsel the patient on strategies to avoid methadone toxicity.
S6.3	The MMT physician shall not allow for any take-home doses during the first four weeks of treatment.
S6.4	The MMT physician shall ensure the reason for all dosage adjustments are documented.
S6.5	The MMT physician shall ensure that the starting methadone dose for all patients is 30 mg or less.
S6.6	The MMT physician shall ensure that the starting methadone dose for patients at higher risk for methadone toxicity is 20 mg or less.
S6.7	The MMT physician shall ensure that the starting methadone dose for patients who have been recently abstinent from opioids is 10 mg or less.
S6.8	The MMT physician shall assess the patient at least weekly during early stabilization.
S6.9	The MMT physician shall assess the patient in-person prior to each dose adjustment.
S6.10	For patients who are not at higher risk for methadone toxicity, the MMT physician shall prescribe dose increases of no more than 10-15 mg every 3-5 days during the early and late stabilization phases.
S6.11	For patients at higher risk of methadone toxicity, the MMT physician shall prescribe dose increases of no more than 5-10mg every 3-5 days during the early and late stabilization phases.
S6.12	For patients who have recently been abstinent, the MMT physician shall prescribe dose increases of no more than 5 mg every five or more days during the early and late stabilization phases.
S6.13	The MMT physician shall not increase the patient's dose more than 10 mg every 5- 7 days during the maintenance phase or once the patient has reached a dose of 80 mg.
S6.14	If the patient misses two or more consecutive doses during the early stabilization phase, the MMT physician shall cancel all subsequent doses, assess the patient in person, and restart the patient maintaining this dose for at least three consecutive days.
S6.15	The MMT physician shall reduce the dose to 30 mg or less when a patient has missed 4 or more doses of methadone during the late stabilization and maintenance phases.
S6.16	The MMT physician shall reduce the dose by 50% or to a dose of 30mg or less when a patient has missed 3 consecutive days during the late stabilization and maintenance phases.
S6.17	During the late stabilization phase, when the patient's dose of methadone is still changing, the MMT physician shall see and assess the patient at least once weekly. The MMT physician shall increase the dose by no more than 5-15 mg every 3-5 days, depending on the patient's cravings, opioid use, withdrawal symptoms, and underlying risk for toxicity.
S6.18	The MMT physician shall order an ECG with a calculated QTc interval for patients on doses above 150 mg.

►Guidelines

G6.1	During initiation and early stabilization, the MMT physician should avoid prescribing any sedating drugs. The MMT physician should also advise the patient to avoid any new sedating medications/drugs.
G6.2	For patients who are addicted to high daily doses of benzodiazepines, the MMT physician should taper either before MMT initiation, or small tapering doses should be given during initiation, preferably in a supervised setting in consultation with an addiction medicine physician.
G6.3	The MMT physician should ensure doses are only increased after the patient has been assessed in person, and it is determined that the patient is experiencing cravings or ongoing opioid use, and/or a constellation of withdrawal symptoms.
G6.4	During the Maintenance Phase, the MMT physician should assess patients weekly to monthly based on the recovery needs of the patient. Patients on contingency management should be assessed more frequently (i.e. weekly). Patients on contingency management with full take-home doses may be assessed less frequently than once a week with long term abstinence of 6 months of more. MMT physician assessments less frequently than once monthly may occur if the patient is well known to the MMT physician, has been clinically stable and abstinent for a long period of time (i.e. years), and is considered by the MMT physician to be a reliable historian.
G6.5	The MMT physician should identify and manage risk factors for Torsades de Pointes arrhythmias, and should obtain an ECG above 120 mg for patients with these risk factors.
G6.6	The MMT physician should repeat the ECG if the patient is at a dose approaching 180–200 mg.
G6.7	The MMT should consider tapering the dose if it is high and if the patient reports sedation or other cognitive effects.
G6.8	When considering assessing a patient for a dose increase, the MMT physician should assess the patient for other conditions that are commonly confused with withdrawal symptoms.
G6.9	If the patient has emesis after taking methadone, the MMT physician should not replace the dose unless the emesis was witnessed by the pharmacist or staff, and it occurred less than 15 minutes after consumption. The replacement dose must be no more than 50% of the regular dose.

6.2 Writing a Methadone Prescription

Safe dispensing of methadone begins with a well-written prescription. Collaboration and communication between the physician and the pharmacist help to enhance patient safety. See Appendix F Sample Prescription Form.

The prescription shall specify all of the following:

1) Start and end dates
2) Days of week that are to be supervised
3) Take Home doses: number of take-home doses and days of week that are to be given as take-home doses
4) Methadone dose: written in both numbers and words to help to prevent tampering of prescriptions.

6.3 Strategies to Reduce Risk of Overdose

- **Patient education.**
  1) Explain to the patient that it takes several weeks to reach the optimal dose of methadone, and it may be dangerous to try to relieve withdrawal symptoms with benzodiazepines, illicit methadone or other drugs.
  2) Advise the patient to:
     - limit his or her driving or use of machinery after a dose increase, particularly in the first few hours after dosing.
     - take the methadone dose in the morning, since the risk of overdose is increased at night (Wolff 2002).
  3) Whenever feasible (with the patient's consent), a family member or significant other should be educated about the symptoms of overdose with clear instructions to seek urgent medical help at the first sign of toxicity. A patient information guide may be used for this purpose (see Appendix I Managing Potential Methadone Overdose)**.**

- **Frequency of visits.**
  Schedule patient visits at least every 1-2 weeks. However, twice-weekly visits during the first two weeks of treatment are recommended, particularly if the patient is at increased risk for methadone toxicity. The physician can schedule an assessment of the patient two to six hours after the methadone dose if there are concerns about sedation with the dose. The physician should inquire about sedation and other side effects.
- **Take-home doses during initial titration.**
  No take-home doses shall be granted during the first month of treatment including Sunday take-home doses, holiday carries, pharmacy closure (see Section 8.0 Take-Home Doses).

- **Sedating Drugs.**
  Avoid prescribing sedating drugs and warn the patient to avoid using them. This includes alcohol, benzodiazepines, non-benzodiazepine hypnotics, antipsychotics, antidepressants, gravol and sedating antihistamines. Even moderate, therapeutic doses of these drugs may increase the risk of overdose if they are initiated at the same time as methadone and the patient is not fully tolerant to their sedating effects. Patients should also be advised to avoid alcohol during MMT initiation.

- **High-dose Benzodiazepine users.**
  Benzodiazepine abuse and dependence are common in this population. As with opioids, it is difficult to accurately judge a patient's benzodiazepine use and tolerance, therefore, benzodiazepine tapering, while difficult on its own, can be very complicated and potentially unsafe (due to oversedation) when attempted with methadone initiation. If possible, patients addicted to high doses (50 mg of diazepam equivalent per day) should be tapered prior to methadone initiation. Otherwise, benzodiazepine tapering**,** during initiation should be considered, with monitoring in a medically supervised setting. Only small benzodiazepine doses should be used, just enough to prevent severe withdrawal. Consultation with an addiction medicine physician is advised.

- **Communication with the pharmacist.**
  Written treatment agreements and regular verbal communication about the patient's clinical presentation to both providers and pharmacists may enhance patient safety.

- **Intoxication or sedation at the pharmacy.**
  At any stage of MMT, the pharmacist should be instructed to hold the methadone and alert the physician if the patient appears sedated or intoxicated.

- **Careful assessment prior to dose increases.**
  Several criteria should be considered increasing the dose of methadone.

6.3.1 Clinical Criteria for Dose Adjustment

The physician should consider increasing the dose if the patient has daily cravings, ongoing opioid use, or opioid withdrawal symptoms. See Appendix H Sample Addiction Medicine Clinical Note. Withdrawal symptoms vary between patients. See Table 04. Most patients report a combination of the following:

Table 04: Withdrawal Symptoms

Physical Symptoms	Psychological Symptoms
Myalgia	Insomnia
Sweating	Fatigue
Yawning	Anxiety
Rhinitis	Irritability
Restlessness	Nausea

Symptoms usually begin a predictable number of hours after the methadone dose, although there may be some daily variation with the patient's activity level and other factors. With each dose increase, the onset of symptoms is delayed and their severity is lessened. Alternative explanations should be sought if the patient has one isolated symptom (such as insomnia or nausea), or if the patient reports that the onset of symptoms is not related to the time of the dose.

The physician should also enquire about side effects, such as constipation and sedation, as this may affect dosing decisions.

6.3.2 Documentation for Dose Adjustments

At visits where the dose is adjusted, the physician should document:

1) Cluster of withdrawal symptoms
2) Timing of withdrawal symptoms (what time of day they appear)

3) Ongoing drug use and timing of drug use:
   - opioid use at the end of the day may indicate inadequate methadone dose.
   - Use of alcohol or benzodiazepines may indicate the need for caution in dose adjustment.
4) Changes in mood and daily activities.

6.4 The Initial Methadone Dose

The physician should base the initial dose on the patient's underlying risk for methadone toxicity. The following factors increase this risk see Table 03: Patient Factors that Increase Risk of Methadone Toxicity (Albion et al. 2010; Srivastava and Kahan 2006).

Sedating drugs include over-the-counter medication such as gravol, prescribed medications such as antipsychotics and sedating antidepressants, or drugs of abuse such as ketamine and GHB. Even therapeutic doses of benzodiazepines can increase risk of methadone toxicity. The MMT physician should look for evidence of benzodiazepine use in the initial drug screen.

Opioid tolerance is difficult to establish by history, so, if in doubt, it is safer to initiate on a lower dose. Lowered tolerance is likely in patients who report non-daily opioid use, daily use of codeine, or daily use of oral opioids at moderate doses. Typically, patients who use opioids intranasally (ie snorting) have a lower tolerance than patients who inject opioids. Tolerance is lower in patients who have been abstinent for more than a few days, e.g., patients who have been recently discharged from a correctional facility, withdrawal management centre or treatment centre. See Table 05.

Table 05: Initial Methadone Dose

Patient Factors	Initial Dose
Higher risk for methadone toxicity	20 mg or less
Recent abstinence from opioids	10 mg or less
No risk factors or recent abstinence	30 mg or less

6.5 Early Stabilization Phase (0-2 weeks)

Dose increases during the early stabilization phase should take place only after an in-person MMT physician assessment and for patients who are experiencing cravings, ongoing opioid use, and/or a cluster of opioid withdrawals symptoms. MMT physicians should assess patients at least once weekly during this phase. See Table 06.

Table 06: Dosing During Early and Late Stabilization Phase

Patient Factors	Dose Increase	Frequency
Higher risk for methadone toxicity	5-10 mg	Every 3-5 days
Recent abstinence from opioids	5 mg or less	Every 5 days or more
No risk factors or recent abstinence	10-15 mg	Every 3-5 days

6.5.1. Missed Doses During Early Stabilization Phase (0-2 weeks)

During the early stabilization phase, patients should be on the same dose for at least 3 consecutive days with no missed doses before an increase. The pharmacists should be advised to contact the MMT physician if the patient misses any doses. If two consecutive doses are missed during the early stabilization phase, the pharmacist should be advised to cancel the prescription until the patient can be reassessed by the physician. Collaborative communication between the physician and pharmacist if the patient misses any doses during early stabilization is essential. The patient must be reassessed in person by the physician and restarted at 30 mg or less.

6.6 Late Stabilization Phase (2-6 Weeks)

Most patients in the late stabilization phase are taking between 50–80 mg of methadone. Most patients during this phase are experiencing only partial relief of withdrawal symptoms, and they often continue to use opioids sporadically.

Dose increases during the late stabilization phase shall be the same as during early stabilization phase (see Table 06) until a dose of 80 mg is reached. Dose increases during the late stabilization phase should take place with an in person MMT physician assessment and for patients who are experiencing cravings, ongoing opioid use, and/or a cluster of opioid withdrawal symptoms. MMT physicians should assess patients at least once weekly during this phase.

6.6.1 Dosing During Late Stabilization Phase

See Table 06: Dosing During Early and Late Stabilization Phase.

6.6.2. Missed Doses During Late Stabilization Phase

If three or more consecutive doses are missed during the late stabilization phase, the pharmacist should be advised to cancel the prescription until the patient can be reassessed by the MMT physician. The patient must be reassessed in person by the MMT physician. After 3 consecutive days missed, the dose should be decreased to 50% of the current dose or 30mg. After 4 or more consecutive days missed, the dose should be decreased to 30 mg or less.

See Table 08 Management of Missed Doses.

6.7 Maintenance Phase (6+ Weeks): The Optimal Methadone Dose

The optimal maintenance dose of methadone will relieve withdrawal symptoms, block opioid-induced euphoria and reduce opioid cravings for 24 hours, without causing sedation or other significant side effects. With experience, the MMT physician can reach this dose for the majority of their patients within 2-8 weeks of initiating MMT. The optimal dose range for most MMT patients is 60-120 mg (Bao et al. 2009; Department of Health (England) 2007; WHO 2009). A meta-analysis by Bao et al reported that doses of methadone between 60-120 mg and individualization of doses are associated with better retention in MMT (Bao et al. 2009).

During the maintenance phase (when the dose is 80 mg or more) the MMT physician shall increase the dose by no more than 5-10 mg every 5-7 days.

Dose increases during the maintenance phase should take place with an in person MMT physician assessment and for patients who are experiencing cravings, ongoing opioid use, and/or a cluster of opioid withdrawal symptoms. MMT physicians should assess patients once weekly when ongoing dose adjustments are occurring and less frequently thereafter if required.

6.7.1. Missed Doses During Maintenance Phase

Standards for missed doses during maintenance are the same as those for late stabilization. See Section 6.9 Managing Missed Doses and Table 08 Management of Missed Doses.

6.7.2 Doses Below 60 mg

There is evidence that methadone doses of 60–100 mg are more effective than doses below 60 mg in reducing heroin use and retaining patients in treatment (Bao et al. 2009; Caplehorn and Bell 1991; Faggiano et al. 2003). However, maintenance doses below 60 mg are justified for patients who have no unauthorized opioid use, report no significant withdrawal symptoms or cravings, are at high-risk for methadone toxicity, or are on a tapering protocol.

6.7.3 Doses Above 120 mg

6.7.3.1 Risks of High Methadone Doses

Opioids such as methadone have several side effects that may be dose related, including sedation, overdose leading to death, sleep apnea and sexual dysfunction. High methadone doses are also associated with prolonged QT interval, which can cause Torsades de Pointes, a ventricular arrhythmia (Abramson et al. 2008; Pimentel and Mayo 2008). One study found that approximately 5% of patients on MMT had QTc > 500 msec, the value associated with increased mortality. All of these patients were on doses in excess of 120 mg (Anchersen et al 2009). Other risk factors for Torsades include, use of cocaine and other stimulants, heavy alcohol consumption, cardiomyopathy, previous MI or valvular abnormalities, a family history of long QT syndrome, liver dysfunction, electrolyte disturbances and medications that affect methadone levels or the QT interval (Abramson et al. 2008; Ehret et al. 2006; Fareed et al. 2010; Justo et al. 2006; Krantz et al. 2009). See Table 07.

6.7.3.2. Assessment and Monitoring

High doses of methadone can sometimes have sedating effects that may not be apparent in the physician's office. The MMT physician should inquire about whether the patient or the patient's family has observed cognitive effects such as 'nodding off,' lethargy, diminished concentration or memory.

At baseline, the physician should identify risk factors for torsades, such as heart disease, family history of sudden cardiac death, or concurrent use of medications that affect QT interval (See Table 07 Risk Factors for QTc Prolongation in Patients on Methadone). An ECG shall be done on patients whose dose is greater than150 mg (Byrne 2009; Girgis 2009) and repeated for doses of 180-200 mg. Patients with known risk factors for Torsades should have an ECG at a dose above 120 mg.

Table 07: Risk Factors for QTc Prolongation in Patients on Methadone

Adapted from: Methadone – associated QTc prolongation: A case report and review of the literature. (Abramson DW, Quinn DK, Stern TA. Prim Care Companin J Clinic Psychiatric 2008; 10(6): 470-476

Risk Factor	Examples
Older Age	
Structural heart disease	Myocardial infarction, congestive heart failure, valvular disease, cardiomyopathy
HIV infection	
Low potassium level	On drugs that lower potassium eg. Diuretics
Low prothrombin level	
On medications that inhibit Cytochrome p450 3A4	HIV antivirals e.g. indinavir Antifungals e.g., Fluconazole, ketoconazole Calcium channel blockers e.g., Diltiazem, verapamil Antimicrobials e.g., Norfloxacin Antidepressants e.g., Fluvoxamine Contraceptives e.g., Mifepristone Foods: e.g., grapefruit juice
Alcohol use	
Cocaine use	
Family or past history of long QT syndrome	History of syncope or sudden cardiac death in the family
On medications that prolong QTc	Cardiac medications e.g., amiodarone, sotalol Antipsychotics e.g., chlorpromazine, haloperidol, pimozide, thioridazine Antibiotics e.g., clarithromycin, erythromycin Anti-nausea drugs e.g., domperidone

6.7.3.3 Management of High Doses

A trial of tapering is indicated for patients who report sedation when on high doses. Clinical experience suggests that tapering to an overall dose decrease of 20-40 mg is tolerated well, and patients often report that they feel more alert and energetic.

The patient should be closely monitored if the QT interval is elevated (> 450 msec for men, > 470 msec for women). Cardiology referral and/or methadone dose reduction should be considered when the QTc exceeds 500 msec, and the MMT physician should take steps to modify risk factors when possible.

6.7.3.4. Ongoing Withdrawal Symptoms in Patients on High Doses

Patients with ongoing withdrawal symptoms despite high methadone doses require ongoing assessment by the MMT physician. Possible causes include:

Rapid metabolism of methadone
- Although controversial, peak and trough levels might be useful in patients who continue to report withdrawal symptoms despite doses of 120 mg or higher.

Use of medications that increase the metabolism of methadone
- Medications suchs as Phenytoin, chronic alcohol use.

Continued opioid use
- Causes increased tolerance and withdrawal symptoms on opioid cessation.

Dose diversion
- The patient consumes some of his/her take-home dose and sells the rest.

Pseudonormalization
- After a methadone dose increase, some patients experience very mild mood elevation. They develop tolerance to this effect after a few weeks, prompting them to seek another dose increase.

Insomnia, anxiety, fatigue and other psychiatric symptoms
- Because psychiatric symptoms are such a prominent feature of opioid withdrawal, patients may incorrectly attribute these symptoms to withdrawal.

Cocaine use
- Cocaine is a methadone inducer (increases the metabolism of methadone) especially when used in large doses. Ongoing use of cocaine may result in the patient complaining of the need for a dose increase. The physician may want to discuss the benefits of abstinence from cocaine.

Pregnancy
- See Section 13: MMT During Pregnancy.

6.8 Split Doses

Split dosing is commonly used during the management of pregnancy or chronic pain, or in patients on medications that induce rapid metabolism of methadone (See Sections 11.2.4, 11.2.5, 11.2.5.2, 13.3.2.2 and Appendix B).

6.9 Managing Missed Doses

Missed doses may indicate a variety of problems, including relapse to alcohol or other drug use. Therefore, the physician should reassess the patient's clinical stability. Pharmacists should report missed doses to the MMT physician in a timely fashion. A clinically significant loss of tolerance to opioids may occur within as little as 3 days without methadone; therefore the MMTphysician should reduce the methadone dose in patients who have missed three consecutive days. The dose can be rapidly increased once the response to the lower dose is assessed. See Table 08 Management of Missed Doses.

Table 08: Management of Missed Doses

Phase of Treatment	Missed Doses	Action	Dose Change
Early Stabilization (0-2) weeks	1 day missed	No dose increase	• Resume same dose. • Do not increase dose until 3 consecutive days at the same dose.
	2 consecutive days missed	• Reassess patient in person. • Cancel remainder of prescription	• Restart at initial dose (10-30 mg) for at least 3 days • Reassess after 3rd consecutive dose.
Late Stabilization/ Maintenance	1-2 days missed	• Provide usual prescribed dose if patient is not intoxicated. • Assess patient in 1-2 weeks to determine clinical stability	• No change
Late Stabilization/ Maintenance	3 consecutive days missed	• Reassess patient in person • Cancel remainder of prescription • Reassess every 3-4 days if dose is increased daily	• Restarted at 50% of regular dose or decrease to 30 mg • Then increase dose to no more than 10 mg daily for maximum of 3 days, then reassess by day 3-4. • There after, dose increase of 10-15 mg every 3 -5 days until 80 mg • Then 10 mg every 5-7 days for dose increases above 80 mg
Late Stabilization/ Maintenance	4 or more consecutive days missed	• Re-assess patient in person • Cancel remainder of prescription	• Restart at 30 mg or less • Then increase dose no more than 10-15 mg every 3-4 days until 80 mg • Then increase 10 mg every 5-7 days for dose increases above 80 mg.

6.10 Vomited Doses

Vomited methadone doses are not replaced unless a health professional or staff member directly observes emesis. If the emesis was witnessed by the pharmacist or staff, and it occurred less than 15 minutes after consumption, the dose can be replaced at no more than 50% of the regular dose.

Repeated dosing (i.e. replacement) creates a risk of inadvertent overdose. Underlying causes of the vomiting should be addressed. For pregnant patients or patients with underlying medical

conditions (eg cancer or HIV), the MMT physician may decide to prescribe a replacement dose even if the pharmacy or clinic staff did not observe emesis (See Section 13.3.2.4).

7.0 Urine Drug Screening (UDS)

7.1 Overview

UDS results are one tool to verify patients' self reported substance use, assess response to MMT and determine suitability for take-home doses. Giving take-home doses to methadone patients with drug-free UDS is an effective strategy for reducing opioid and other drug use (contingency management) (Chutuape et al. 1999a; Chutuape et al. 1999b; Iguchi et al. 1988; Preston et al. 2002; Schmitz et al. 1998; Stitzer et al. 1992).

UDS combined with a patient's self-reported drug use are more accurate than either alone. (Perrone et al. 2001; Ries et al. 2002). Frequent UDS may be more likely to detect drug use than occasional UDS (Chutuape et al. 2001, Wasserman et al. 1999). The results of a RCT conducted (Chutuape et al 2001) showed that methadone take-home doses contingent on a minimum of monthly drug-free urines prevents declines in treatment outcomes (38.9% were abstinent for opiates and cocaine for > 8 weeks); better results were achieved by weekly-urine testing (56.6% were abstinent). However, ongoing frequent UDS is costly.

►Standards

S7.1	The MMT physician shall use either point-of-care immunoassay, or chromatography or both for routine screening of illicit opioid use, cocaine, and benzodiazepines.
S7.2	The MMT physician shall obtain and interpret a UDS prior to MMT initiation.
S7.3	The MMT physician shall ensure that each UDS (including UDS collected between office visits) is interpreted in a timely fashion by the MMT physician for the purpose of monitoring and managing the patient.

►Guidelines

G7.1	The MMT physician should consider chromatography testing if the patient uses substances that are difficult to detect with immunoassays (e.g., fentanyl, amphetamines), if the patient disputes the test results, or if the patient faces serious consequences for a positive test (e.g., child custody).
G7.2	The MMT physician should have the UDS collection supervised, if possible, to verify the integrity of the UDS specimen.
G7.3	If supervision is not possible, the MMT physician should ensure other measures such as creatinine or temperature monitoring are implemented.
G7.4	The MMT physician may conduct UDS on a fixed or random schedule.
G7.5	The MMT physician should order frequent (4 times or more per month) UDS: 1) when adjusting the dose during stabilization 2) for contingency management with patients who continue to use drugs but who also wish to eventually achieve take-home doses. 3) for contingency management with patients who have already achieved abstinence and are in the take-home dose acquisition phase.
G7.6	The MMT physician may order less frequent UDS (1-3 times per month) if the patient has abstained consistently from illicit drug use for at least 6 months or for patients not working toward take-home doses (e.g., due to ongoing drug use or homelessness). In some circumstances, less than monthly urine testing may be acceptable.
G7.7	The MMT physician should take into consideration treatment benefits as well as the effect on treatment retention where weekly UDS is used during the Maintenance Phase.
G7.8	For patients on take-home doses who meet the criteria for less frequent UDS, the MMT physician should consider increasing the frequency of UDS (4 times or more per month) for 1 to 3 months if the patient shows signs of lapse or relapse, for the purpose of contingency management and ongoing adjustment of take-home doses. The frequency may be reduced accordingly based on the response of the patient.

7.2 Initial UDS

Initial UDS results should confirm the presence of opioids and, whenever possible, identify the patient's primary opioid of abuse. Either a broad-spectrum initial analysis or an opioid-specific immunoassay may be used. If immunoassay is used, it should test for the specific opioid abused by the patient. However, a general opioid immunoassay that fails to identify a patient's specific opioid may be sufficient to initiate a patient on methadone if there is strong clinical evidence that the patient is opioid dependent (e.g., obvious opioid withdrawal signs and symptoms and/or IV track marks, corroborating information from a physician, or previous MMT). See Table 09.

If the initial UDS is inconsistent with the patient's reported opioid use (e.g. the patient reports daily oxycodone use and the oxycodone is negative in the UDS), the MMT physician should conduct a more thorough assessment to confirm a diagnosis of opioid dependence prior to initiating MMT.

Table 09: Point-of-Care Testing (EMIT) vs Chromatography

Test	Advantages	Disadvantages
Point-of-Care Testing (EMIT)	• More sensitive than chromatography • Detects opioids for 2-4 days • Immediate results	• Does not distinguish or differentiate specific types of opioids, except for oxycodone • Synthetic opioids, such as fentanyl, are often missed.
Chromatography	• Can identify specific opioids; • More specific than immunoassay; • Can identify TCA, antipsychotic, gravol.	• Detects opioids for 1-2 days; • Less sensitive than immunoassay • Delayed results

7.3 UDS Collection Schedule

7.3.1 Frequent UDS during Stabilization Phase

Frequent UDS is defined as 4 times per month or more.

Frequent urines may be collected once to twice a week during the stabilization phase. Twice weekly urines will more likely detect sporadic drug use and in some patients might facilitate more accurate self disclosure. The MMT physician should ensure that frequent twice weekly urines do not interfere with the patient's work or family obligations.

7.3.2 Frequency of UDS during Maintenance Phase

Many patients in maintenance phase benefit from ongoing weekly UDS for the purpose of ongoing monitoring and management of their addiction disease which is characterized by periods of abstinence and relapse. Frequent UDS may be collected once to twice per week during the maintenance phase for patients who are interested in having take-home doses or who are in the take-home dose acquisition phase. Take-home doses are an essential component of long term success for patients during the maintenance phase. The UDS result combined with counselling can be an effective tool to help curtail illicit drug use especially during the take-home acquisition phase.

Once full take-home doses have been achieved, or the patient has been consistently abstinent for 6 months or more, the frequency of UDS may decrease to twice to once monthly depending on the recovery needs of the patient.

Some patients who have achieved full take-home doses may benefit from more frequent UDS as they consider it integral to their sustained abstinence. The MMT physician should balance these issues with the consideration that collecting weekly UDS may be inconvenient to the

patient and therefore may lead to a reduction in treatment retention. Collecting more than 4 urines per month for patients on full take-home doses is not indicated.

Less frequent than weekly urine testing may also occur for patients on chronic prescribed benzodiazepines who are not eligible for more than one take-home dose.

In occasional circumstances, patients including those who have take-home doses, may provide UDS less often than once monthly if they are well known to the MMT physician over a number of years, they have long established clinical stability and drug use abstinence and are considered by the MMTphysician to be reliable historians. Less than monthly urine testing may also occur for patients who have ongoing drug use or who are chronically homeless and will not be seeking take-home doses.

7.3.3. UDS Frequency during Relapse or Return to Drug Use for Patients on Take-home Doses

If the patient slips or relapses after a prolonged period of abstinence, the frequency of UDS should be increased to weekly for one to three months and take-home doses should be reassessed (see Section 8.6). Contingency management combined with counselling and support is essential in helping patients quickly recover from a relapse and preventing it from becoming sustained.

8.0 Take-Home Doses

8.1 Overview

Take-home doses are key to the success of MMT. Controlled trials have demonstrated that MMT patients markedly reduce their use of heroin and cocaine when given take-home doses for UDS free of illicit drugs (contingency management) (Chutuape et al. 1999a; Chutuape et al. 1999b; 2001; Iguchi et al. 1988; Preston et al. 2002; Schmitz et al. 1998; Stitzer et al. 1992). There is strong evidence that methadone take-home doses contingent on drug-free UDS prevent the decline in treatment outcomes over time. Abstinence can be sustained with UDS conducted monthly; weekly UDS produces even better results (Chutuape et al. 2001) Surveys and observational studies have found that patients strongly value take-home doses, and treatment retention rates are lower in clinics with restrictive take-home policies (Amass et al. 1996; Amass et al. 2001; Pani et al. 1996).

►Standards

S8.1	When prescribing take-home doses, the MMT physician shall ensure that patients understand how to store their methadone securely, that they understand the risks of diverted methadone, and that they agree never to give or sell even part of their dose to others.
S8.2	The MMT physician shall not prescribe take-home doses if: 1) the patient is at risk of taking more than prescribed, due to an untreated mental illness or cognitive impairment 2) the patient is not able to safely store the methadone 3) there is reasonable evidence that the patient is diverting methadone 4) the patient does not understand the risks of methadone diversion.
S8.3	The MMT physician shall prescribe an accelerated take-home schedule only if: 1) prolonged daily pick-up is likely to cause the patient to drop out of treatment because of lack of transportation or work or family commitments 2) the patient is able to safely store the medication 3) the patient does not have an active addiction or mental illness that increases the risk of methadone misuse or diversion.
S8.4.	The physician may prescribe a Sunday take-home dose after four weeks (rather than eight weeks) only if the patient: 1) is able to safely store the medication 2) does not have an active addiction or mental illness that increases the risk of methadone misuse or diversion 3) lives in a community that does not have a pharmacy that is open on Sunday 4) has no hospital available for Sunday dispensing 5) does not have transportation to a pharmacy in a different community.
S8.5	The MMT physician shall prescribe take-home doses that are exceptions to the take-home dose schedule ("special carries") only if: 1) the patient is able to safely store the medication and has good insight for carry safety issues 2) the patient is emotionally stable and displays good judgment to recognize the risks for methadone misuse or diversion
S8.6	The MMT physician shall reduce the level of take-home doses if the patient has a sustained relapse to problematic substance use.
S8.7	The MMT physician shall cancel all take-home doses abruptly in the circumstances listed below. The daily observed dose should be reduced if the MMT physician suspects the patient may not have been taking the full take-home dose. 1) There is reasonably strong evidence that the patient has diverted their methadone dose, or has tampered with their UDS. 2) The patient has missed 3 or more days of methadone (except in unavoidable circumstances such as hospitalization). 3) The patient has become homeless or in unstable housing, and can no longer safely store their methadone. 4) The patient is actively suicidal, cognitively impaired, psychotic, or is otherwise at high risk for misuse of their methadone dose. 5) The patient has recently been released from jail when incarcerated for prolonged periods of greater than 3 months.

►Guidelines

G8.1	Prior to prescribing the first take-home dose, the MMT physician should instruct the patient to show a locked box that will be used for the transportation and storing of take-home doses.
G8.2	The MMT physician should ensure the first weekly take-home dose is prescribed only after the patient has been in the program for two months, and prior to take-home dose acquisition the patient has had at least one week without problematic substance use, as determined by history and UDS.
G8.3	The MMT physician should prescribe additional take-home doses at a rate of no more than one dose per week every four weeks, to a maximum of six take-home doses per week. Each additional take-home dose should be prescribed only after the patient has had at least four weeks without problematic substance use. (see Table 10 Problematic versus Non-Problematic Drug Use)
G8.4	In the accelerated schedule, the MMT physician may prescribe the first carry after four weeks, and subsequent carries at a rate of no more than one extra take-home dose per week, every 2-3 weeks, to a maximum of six take-home doses per week.
G8.5	In the accelerated schedule, the MMT physician should prescribe the extra weekly take-home dose only if the patient has had at least two consecutive weeks without problematic drug use.
G8.6	The MMT physician should prescribe the Sunday dose at an alternate pharmacy if the patient's regular pharmacy is closed on Sunday.
G8.7	The MMT physician should instruct the patient to bring a receipt to the alternate pharmacy to verify that they received their doses.
G8.8	MMT physicians working in communities without a pharmacy open seven days per week should consider negotiating with the local hospital to provide Sunday dispensing, or arranging for a nurse or pharmacist to dispense the methadone at the MMT Clinic (Delegation Exemption).
G8.9	The MMT physician may give special carries only on compassionate grounds for patients who are not yet receiving take-home doses. The patient should be on MMT for at least one month, and a maximum of seven carries should be given at a time.
G8.10	The MMT physician may give special carries for sound personal reasons or holidays for patients who have markedly reduced their substance use, are approaching a stable methadone dose, and are receiving 1-2 take-home doses/week. A maximum of seven carries should be given at a time. The MMT physician should ensure that the previous carry level is resumed after the period of special carries.
G8.11	The MMT physician may give special carries for work or vacation travel for patients who have not had problematic drug use for months, are clinically stable and receiving 3-6 take-home doses per week. A maximum of 2-4 weeks may be given at a time. The MMT physician should ensure that the previous carry level is resumed after the period of special carries.
G8.12	During a relapse, the MMT physician should gradually reduce the take-home doses at a rate of one take-home dose per week for each week of problematic substance use, as determined by history or UDS. Take-home doses may be reinstated at the same rate, one dose per week for each week without problematic substance use.
G8.13	MMT physicians may prescribe a single take-home dose per week to patients who continue to use substances if they meet all of the following criteria: 1) They are deemed by the MMT physician to be clinically stable. 2) They are able to safely store their medication. 3) They are at a low risk of diversion. 4) Their methadone dose is stable. 5) In the MMT physician's judgment, the drug use does not appear to be causing significant medical, psychiatric or social problems.

G8.14	The MMT physician should consider reducing take-home doses for patients who repeatedly consume them early, or who repeatedly report lost or stolen take-home doses.
G8.15	The MMT physician may reinstate take-home doses immediately for patients who remain clinically stable without problematic drug use, and: 1) had take-home doses cancelled due only to missed doses 2) have been incarcerated for less than 3 months.
G8.16	For patients who have tampered with their UDS in an attempt to conceal a relapse, the MMT physician may reinstate take-home doses after a one month period at a rate of one take-home dose per week to one take-home dose per month depending on the patient's reliability and clinical stability.
G8.17	The MMT physician may decide to restrict carries indefinitely if there has been proven diversion. A second opinion with another MMT physician should be considered before reinstituting the carries.
G8.18	The MMT physician may give at least one take-home dose per week to clinically stable patients who are being prescribed benzodiazepines or opioids.
G8.19	The MMT physician may provide more than one take-home dose per week if the patient: 1) has a medical or psychiatric diagnosis that warrants the use of the benzodiazepine or opioid 2) is on a low-to-moderate therapeutic dose of the benzodiazepine or opioid 3) has not shown signs of benzodiazepine or opioid misuse or toxicity 4) provides consent for the MMT physician to discuss their management with their opioid or benzodiazepine prescriber 5) is prescribed and dispensed the medications in a controlled dispensing fashion 6) meets all other criteria for take-home dose eligibility.
G8.20	The MMT physician should limit the take-home doses of patients who refuse consent to communicate with their opioid or benzodiazepine prescriber.
G8.21	Patients may be given 13 days of take-home doses, if the following criteria are met: 1) They have a documented history of full take-home doses and clinical stability, while on MMT, for 5 years or more. 2) There have been no past reported mishaps with lost or stolen carries. 3) They are working, in school or have daily family commitments that make weekly attendance at a pharmacy difficult. 4) They have been abstinent and clinically stable for most of their time in the program, and they are reliable historians. 5) The methadone dose is 120mg or less.

8.2 Take-Home Doses: Risks

8.2.1 Diversion

Diversion of take-home doses is a serious public health problem. The use of methadone for analgesia has increased sharply in the US, with a seven-fold rise from 1997 to 2004. This has been accompanied by a 17-fold increase in methadone-related deaths (Sims et al. 2007).

The risk of diversion and accidental or intentional misuse increases in patients who:

- have suicidal ideation or cognitive impairment
- are homeless, living in a shelter or transiently housed
- are actively addicted to alcohol, cocaine, benzodiazepines or other drugs.

The last group is at higher risk because they may sell their methadone in order to pay for their drug use, and are at greater risk for overdose due to interactions between methadone and their drug of abuse.

8.2.2 Locked Box

To increase the safety of storing methadone at home, patients can be asked to use locked-boxes (Breslin and Malone 2006).

Before take-home doses are prescribed, the physician should ask patients to bring in a locked box to demonstrate that they are able to store methadone safely. This is particularly important for patients who have children, adolescents or young adults living at home. It is not necessary for patients to bring locked boxes to every pharmacy or clinic visit.

8.3 Take-Home Doses: Criteria

The criteria for determining appropriateness for take-home doses are based on patient and community safety and on clinical stability, where clinical stability can be defined by:

1. Stable dose of methadone (with allowances for occasional dose increases)
2. No recent problematic drug or alcohol use. See Table 10.
3. Compliance with treatment directives
4. Stable housing
5. Emotional stability and good insight into carry safety issues.

Collaborative communication with the pharmacist will facilitate and provide information about the patient's daily clinical presentation and stability.

Table 10: Problematic versus Non-problematic Drug Use

Type	Definition	Patient Behaviour and Symptoms
Problematic Drug Use	Ongoing drug use with negative emotional, social, or financial consequences for the patient.	Unstable mood and relationships; unsafe or illegal activities
Non-problematic Drug Use	Intermittent sporadic drug use without significant adverse consequences	Stable mood and relationships, productive activities (work, family, school).

Prior to prescribing take-home doses, the physician should carefully explain the risks of methadone diversion or misuse, and the patient's responsibility to store and use their dose safely.

A written take-home dose agreement is highly recommended (See Appendix K Take-Home Dose Agreement).

8.4 Take-Home Dose Acquisition Schedules

8.4.1 First Take-Home Dose

Patients are typically eligible for their first weekly take-home dose after at least two months in MMT treatment if they meet the criteria for clinical stability and prior to take-home dose acquisition the patient has had at least one week without problematic substance use, as determined by history and UDS.

8.4.2 Sunday Dosing

For patients with no take-home doses, if the patient's regular pharmacy is closed on Sunday, an alternate pharmacy may be used. The patient should be instructed to present a receipt verifying that they have received their daily doses at the regular pharmacy. This will ensure that patients who have missed doses at the regular pharmacy are not given their full dose at the Sunday pharmacy. Ideally, the physician would collaboratively communicate with the Sunday pharmacist ahead of time to pre-arrange the beginning of take-home dosing on Sundays for their patient.

Some communities do not have a pharmacy that is open on Sunday, forcing patients to travel to a pharmacy in a different community. This can be disruptive and costly, and it may cause some patients to drop out of treatment. Yet any take-home dose in the first few weeks of MMT can be hazardous; unstable patients may take the extra carry early, putting them at high risk for toxicity.

In an attempt to promote treatment retention while reducing the risk of toxicity, the guideline allows for Sunday carries after only four weeks for patients who do not have access to a Sunday pharmacy.

MMT physicians who work in communities without a Sunday pharmacy are encouraged to arrange Sunday dispensing with their local hospital, or to arrange for delegated dispensing. In delegated dispensing, the methadone doses are delivered in advance to the MMT clinic. The clinic opens for 1-2 hours on Sunday, and the methadone doses are dispensed by the clinic nurse or pharmacist according to CPSO policy.

8.4.3 Subsequent Take–Home Dose Acquisition

Subsequent increases in take-home doses occur every 4 weeks with evidence of clinical stability as per Guidelines 8.2 and 8.3. Occasional dose adjustment/increases may occur during take-home dose acquisition provided the patient is clinically stable.

8.4.4 Accelerated Take-Home Schedule

Patients who have regular work, full-time educational programs or family commitments may find it difficult to attend the pharmacy daily, causing them to drop out of MMT. These patients may receive take-home doses at an accelerated rate if they are at lower risk for misuse of their take-home doses, i.e. they are clinically stable, are not currently addicted to other substances and do not have a concurrent active mental illness. The first accelerated take-home dose may be given after one month, with one additional weekly dose every 2-4 weeks. Patients should have at least two consecutive weeks of non-problematic substance use before receiving the next additional take-home dose. Only a minority of MMT patients will likely require accelerated doses.

8.5 Take-Home Doses in Exceptional Circumstances ("Special Carries")

Before prescribing take-home doses for exceptional circumstances, the MMT physician should attempt to verify the patient's personal or family crisis (with corroborating information from a third party) or travel plans, particularly if the MMT physician doesn't know the patient well or is unsure about the patient's reliability. The MMT physician may choose to communicate with the pharmacist to get corroborating information recent patient stability in preparation for "special carries". The previous take-home dose level should be resumed after the period of "special carries". The following criteria are suggested for prescribing exceptional take-home doses. See Table 11.

Table 11: Criteria for Prescribing Exceptional Take-Home Doses

IF:	THEN:
Patient has been on MMT for at least one month but is not yet eligible for any take-home doses.	• Give take-home doses on compassionate grounds only, e.g., a personal crisis or family matters. • Give no more than 7 take-home doses at a time.
Patient has markedly reduced substance use, is approaching a stable methadone dose, and is receiving 1-2 take-home doses/week.	• Give take-home doses for sound personal reasons only e.g., vacation / holidays. • Give no more than 7 take-home doses.
Patient has not had problematic drug use for months, is clinically stable and receiving 3- 6 take-home doses per week.	• Give up to 2-4 weeks take-home doses for travel purposes. • If more than 4 weeks of take-home doses is required, a second opinion with another MMT physician is suggested.

8.6 Reducing Take-Home Doses

8.6.1 Relapse to Problematic Drug Use

A "slip", or a single episode of drug use, does not necessarily require a reduction in take-home doses, unless the patient shows other signs of clinical instability. However, take-home doses should be reduced during a sustained relapse. A contingency management approach,

combined with increased counselling and supportive care, may help the patient recover from a relapse before it causes serious physical or social damage. With contingency management, the frequency of UDS is increased to weekly, the intensity of counselling and follow-up is increased, and take-home doses are reinstated at a gradual rate of one take-home dose per week as the relapse resolves.

Patients who have had a prolonged relapse of greater than twelve months and have now stopped problematic drug use should have take-home doses introduced at the same rate as new patients, i.e. one take-home dose per week per month.

8.6.2 Reducing or Cessating Take-Home Doses for Reasons Other than Substance Use

The MMT physician should consider reducing take-home doses if the patient repeatedly consumes take-home doses early, or repeatedly reports lost or stolen take-home doses. Some patients, especially those with mental health issues, or addiction recovery needs, may benefit from increased structure of observed dosing at the pharmacy, and therefore decreased take home doses.

If the patient has tampered with their UDS in an attempt to conceal a relapse, the physician should cancel take-home doses immediately, and reinstate the take-home doses after a one month period at a rate of one take-home dose per week to one take-home dose per month depending on the reliability of the patient, and demonstrated abstinence.

Patients for whom there is strong evidence of diversion should have their take-home doses restricted indefinitely, as there is no reliable method to prevent diversion if their take-home doses are reinstated. A second opinion with another MMT physician should be sought prior to reintroduction of the take-home doses.

Take-home doses should also be cancelled in patients who no longer have stable housing, have missed three or more days of methadone (except in unavoidable circumstances), or they have a mental illness that places them at high risk for misuse of take-home doses. Because patients who have been incarcerated for prolonged periods (3 months or more) are often clinically unstable on release, they should have daily dispensing of methadone in the first week after discharge from jail even if they had take-home doses prior to their incarceration. Once clinical stability has been reestablished, the take-home doses may be reinstated at a rate of one take-home dose per week.

In certain circumstances, take-home doses may be reinstated at the previous level one week later if the doses were abruptly cancelled because the patient missed three or more doses, or because the patient was incarcerated for less than 3 months. In either case, the take-home doses should only be reinstated if the patient remains clinically stable and is not using drugs problematically.

8.7 Take-Home Doses for Patients on Benzodiazepines or Opioids

At least one take-home dose per week may be prescribed to clinically stable patients who are on benzodiazepines or opioids. More than one-take-home dose per week may be prescribed under circumstances listed above in Guidelines 8.18, 8.19 and 8.20.

Regardless of the level of take-home doses, the MMT physician should periodically attempt to taper the benzodiazepine or opioid, particularly if the dose is high (daily equivalent of diazepam 50 mg/day, or morphine 200 mg per day) see Section 11.4 Benzodiazepines.

MMT physicians should not prescribe take-home doses for patients who refuse consent to contact the opioid or benzodiazepine prescriber. The MMT physician may also taper and discontinue the methadone if there is a strong possibility that the patient is misusing the medications or is on an unsafe combination. The MMT physician may contact the other non-MMT prescriber without the patient's consent if there is an imminent risk of harm.

8.8 Routine 13 Day Take-Home Doses for Work Commitments

In occasional circumstances, some patients who are on six take-home doses, who have work schedules that make it difficult to go to the pharmacy for weekly dispensing may benefit from extended two week take-home doses on a regular basis if the criteria in Guideline 8.21 are met.

9.0 Voluntary and Involuntary Withdrawal from MMT

9.1 Overview

Withdrawal from MMT is most likely to be successful if the patient has been abstinent from illicit substances for a substantial period of time, does not have current or untreated psychiatric co-morbidity, and has strong social supports and counselling (Magura and Rosenblum 2001). The patient should have a major role in deciding the rate of the taper. A systematic review by Amato et al., evaluated the effectiveness of methadone tapers compared to LAAM, buprenorphine and clonidine in managing opioid withdrawal and on completion of detoxification. Overall methadone tapers were as effective as other pharmacological agents used for detoxification from opioids (Amato et al. 2005).

►Standard

None for this section

►Guidelines

G9.1	For voluntary tapers, the MMT physician should taper patients slowly. The rate of the taper should be patient driven, even if the patient desires a more rapid taper.
G9.2	The MMT physician should attempt to decrease the dose more slowly at doses below 20-30 mg, as withdrawal symptoms become more pronounced.
G9.3	The MMT physician should identify patients who are good candidates for a successful methadone withdrawal, and discuss the risks and benefits of withdrawal with them.
G9.4	The MMT physician should decrease the methadone dose slowly. The decrease should be stopped or reversed at patient request or if the patient experiences severe dysphoria, cravings, or withdrawal symptoms, or relapses to opioids or other drugs.
G9.5	The MMT physician should see the patient regularly during the decrease, to assess the patient's mood and withdrawal symptoms, and to provide supportive counselling.
G9.6	The MMT physician should offer to follow the patient for at least a few months after completion of the decrease.
G9.7	The MMT physician should warn the patient about the loss of tolerance and the risk of toxicity if they relapse to opioids.
G9.8	The MMT physician should offer to reinstate MMT if the patient requests it during voluntary withdrawal.
G9.9	The MMT physician may transfer or cessate a patient from MMT if: a) the patient has been threatening or disruptive b) the patient is consistently non-compliant with the treatment agreement c) the patient is at high risk for methadone overdose and attempts to reduce the risk have failed.
G9.10	The MMT physician should explain the reasons for cessation and offer to transfer the patient to another MMT physician.
G9.11	The MMT physician should decrease the methadone dose and assist the patient in seeking alternate care (e.g., an abstinence based program) if a transfer is not feasible.
G9.12	For an involuntary taper, the MMT physician should decrease the methadone dose at a rate of no more than 10 mg every three to four days.
G9.13	The MMT physician may use pharmacotherapy in the final 1-2 weeks of the decrease to relieve withdrawal symptoms.
G9.14	The MMT physician should encourage the patient to engage with another health care professional or addiction treatment program for counselling and support.

9.2 Voluntary Withdrawal

Patient-centered tapering has reasonably good success rates. In one study, 46% of subjects remained abstinent after an average of 2.4 years post-MMT (Cushman, 1978). Success rates are higher for patients who have been on MMT for two years or more (Cushman 1981; Hubbard et al. 2003; Stimmel et al. 1978). Factors that increase the chances of success are:

- long-standing abstinence from drugs of abuse
- no current mental illness
- a supportive social network.

The rate of the taper should be negotiated with the patient, and should be stopped or reversed at the patient's request if the patient experiences severe cravings, dysphoria, withdrawal symptoms, or relapse to substance use. In general, slow tapers are more successful than rapid tapers (Senay et al. 1977). The daily dose should generally be decreased by no more than 5 mg to 10 mg every 1-2 weeks, or decrease 10% of previous dose.

Withdrawal can trigger an organic mood syndrome, which may become more severe as the dose falls below 20-30 mg/day (Kanof et al., 1993). In this case a gradual decrease of 1-2 mg every few weeks can be used.

9.3 Involuntary Withdrawal

9.3.1 Indications for Involuntary Withdrawal

The decision to transfer or cessate a patient should be documented in detail. The cessation should be based on reliable information, not hearsay or rumor. Indications for cessation include:

- threats to staff members or others
- disruptive behaviour at the methadone clinic
- violent behaviour towards a staff member or others
- non-compliance with patient treatment agreement and program expectations
- diversion of methadone
- high risk for methadone overdose and attempts to reduce the risk have failed. For example, the patient continues to use high doses of benzodiazepines or alcohol, has shown signs of sedation or has required medical treatment for an overdose, and refuses appropriate interventions (e.g. inpatient or outpatient benzodiazepine tapering).

9.3.2 Process for Involuntarily Withdrawing a Patient

Recommendations to effectively end the doctor-patient relationship where MMT is being provided are as follows:

1. If possible, arrange a transfer to another MMT physician.
2. Communicate your decision clearly to the patient. This should include the details of a tapering schedule and/or end date of their methadone prescription.
3. Give the patient a reasonable amount of time to find another MMT physician. This time will vary according to location and circumstances, but should be at least one month.
4. Provide the patient with reasonable help to find another MMT physician. Provide the patient with the CPSO Methadone Program phone number for MMT physicians accepting new patients.
5. Have the patient sign acknowledgement that he or she is aware of the MMT termination or send the patient a registered letter, confirming termination with a return receipt requested and keep a copy in the medical record.

See CPSO Policy entitled *Ending the Physician-Patient Relationship*
http://www.cpso.on.ca/policies/policies/default.aspx?ID=1592

MMT patients who feel that they have been wrongfully dismissed can contact the CPSO Public and Physician Advisory Service to lodge a complaint. The potential for dispute will be reduced if the MMT rules are made clear at the commencement of treatment.

10.0 Counselling and Case Management

10.1 Overview

MMT is more than a pharmacotherapy: it is well documented that case management and counselling services integrated into MMT have positive effects on treatment outcomes (Australian Department of Health and Ageing, 2003; Collège des médecins du Québec & Ordre des pharmaciens du Québec, 2000; Currie, 2001; Farrell et al., 1996; McCann et al., 1994; NIDA, 1999). Counselling enhances treatment retention, decreases patients' use of illegal opioids and other substances and improves patients' overall functioning in terms of criminality, homelessness, mental health and vocational and educational involvement. (Health Canada, 2002)

►Standards

S10.1	The MMT physician shall provide counselling to willing patients or refer them to counselling services in the community while on MMT.
S10.2	The MMT physician shall regularly document how the patient is doing in terms of their overall functioning.

►Guideline

None for this section.

10.2 Treatment Team

Collaborative practice in MMT is considered best practice. Ideally, the MMT patient should have access to a team that includes physicians, nurses, social workers, therapists, psychologists, case managers, peer support workers and pharmacists. Although not all settings and communities are this ideal, the MMT treatment team (at minimum physician and pharmacist) can strive to achieve the best possible outcomes through a collaborative, interprofessional approach.

The Canadian Interprofessional Health Collaborative (CIHC) has published a framework and resources to support interprofessional collaboration. "Interprofessional collaboration is the process of developing and maintaining effective interprofessional working relationships with learners, practitioners, patients/clients/families and communities to enable optimal health outcomes. Elements of collaboration include respect, trust, shared decision-making and partnerships."(CIHC 2010)

Further, the recently released recommendations for mental health and addictions services, the Select Committee on Mental Health and Addictions recommended "Mental Health and Addictions Ontario should ensure that institutional and community-based service providers actively seek to involve peer support workers in all aspects of service delivery. .."(Ontario Select Committee, August 2010)

The CIHC National Interprofessional Competency Framework defines six competency domains for interprofessional collaboration, as follows:

1. Interprofessional communication
2. Patient/client/family/community-centered care
3. Role clarification
4. Team functioning
5. Collaborative leadership
6. Interprofessional conflict resolution

Collaborative patient-centered practice improves outcomes for patients on MMT, as in any other area of health care practice.

10.3 Case Management

Case Management Services are defined as "a process that includes the designation of a primary worker whose responsibilities include the ongoing assessment of the patient and his/her problems, ongoing adjustment of the treatment plan, linking to and coordination of required services, monitoring and support, developing and implementing the discharge plan, and advocating for the patient"(Tschakovsky, 2009).

Case management services are offered regardless where the individual is in the system (Ontario Addiction Services Advisory Council 2000). A case manager's role includes a range of activities including:

1. Coordinating access to treatment
2. Providing information
3. Helping patients gain access to additional health and social services and
4. Advocating for the patient.

10.4 Therapeutic Factors

Methadone alone does not lead to recovery, to be effective, MMT must be an integrated treatment approach that includes counselling and other supports that address the determinants of health.

The factors that lead to successful change have been studied and weighted by Lambert (1992):

1) 40% of a patient's ability to exhibit positive change is attributable to **extra-therapeutic factors** (e.g. safe and stable housing, secure employment, adequate financial resources, positive interactions, supports in the community).
2) 30% is attributable to a patient's experience of the **therapeutic relationship** (e.g. a health care provider's non-judgmental attitude, warmth, respect and caring).
3) 15% is attributable to a patient's sense of hope and expectation for **recovery.**
4) 15% is attributable to the provider's **techniques and skills** (e.g. cognitive-behavioural therapy, mindfulness-based stress reduction).

The rest of this section briefly addresses these four factors.

10.4.1 Extra Therapeutic Factors

Social determinants of health (extra-therapeutic factors), such as housing, income and social support networks, can greatly affect a person's mental health (Tschakovsky, 2009). Providing counselling and case management to MMT patients can be complex: Patients may need help making changes in how they use substances; they may have financial, housing, legal and health problems; and many have histories of trauma, mental health problems or relationship difficulties.

Instability or difficulty in one or more of the following areas may indicate a need for more intensive counselling and help:

Medical and wellness issues may include:

1) Identification and treatment of concurrent mental illness
2) Chronic physical health problems (HCV, HIV, birth control)
3) Pregnancy
4) Issues of abuse – physical, sexual, emotional – and trauma
5) Parenting and family counselling
6) Changing drug and alcohol use
7) Lifestyle changes such as smoking, nutrition, exercise, leisure time.

Life skills and practical help may include:

1) Securing basic necessities, such as housing, food, clothing
2) Legal issues
3) Life skills
4) Coping with stress
5) Social isolation
6) Chaotic lifestyle (frequently missed appointments or doses)
7) Stopping drug use and preventing relapse.

Practical support may include:

1) Support and someone to talk to; general counselling
2) Help with referrals to community resources, filling out forms and applications, providing letters.

10.4.2 Therapeutic Relationship

Research shows that a positive therapeutic relationship between a MMT physician and a patient has a helpful impact. Therapeutic approaches are most successful when there is a strong therapeutic alliance (Gossop et al. 2006; Martin et al. 2000; Tschakovsky 2009). This involves the MMT physician creating a non-judgmental, collaborative environment whereby patients feel safe to discuss their feelings and concerns. Particularly where there are complex psychosocial problems, the MMT physician will need to draw on the support of formal and informal referral and realize the limits of what they can provide. If a MMT physician is not able or prepared to provide counselling, it is essential to connect the patient with services in the community.

10.4.3 Concepts of Recovery

Recovery refers to the ways in which people with mental health and/or addiction problems experience their lives through focusing on positives: health, hope, choices, equity, respect, supports and optimizing their quality of life. More specifically, recovery is about empowerment (having control over one's life); self-determination and personal responsibility; having one's expertise valued; reaching one's potential; engaging in meaningful activities, such as education and work; being included in community life; and having a voice in one's treatment plans.

Excerpted from Overview of health promotion (© 2009 CAMH), accessed on CAMH Knowledge Exchange portal December 2010.
http://knowledgex.camh.net/amhspecialists/promotion/Pages/recovery.aspx

10.4.4 Counselling Techniques and Skills

The evidence for the impact of counselling is very strong. Drucker et al. (2007) recommends that MMT physicians be willing and able to provide counselling to their MMT patients. In a recent survey of MMT patients in Ontario (Tschakovsky, 2009), 27% indicated they received counselling from MMT physicians (either alone or in addition to other support), 18% received counselling from a nurse and 12% received counselling from a psychiatrist (either alone or in addition to services from another agency).

Counselling happens across the continuum of care, from screening and assessment through treatment and relapse prevention. Most change happens in early treatment. Types of counselling that have proven effective in addictions work include Motivational Interviewing (MI) and Cognitive Behaviour Therapy (CBT).

Motivational interviewing is a counselling style that recognizes and resolves patient ambivalence in order to prepare patients to change addictive behaviours. MI elicits change statements and goals from the patient, rather than the counselor. Motivational interviewing has been shown to be particularly helpful in working with people who use substances (Burke 2002). This method focuses on patient's experiences; draws on their concerns, perspectives and values; and encourages patients to evaluate their own life choices and explore the consequences of their choices in a non-judgmental way.

Cognitive-behavioural therapy (CBT) is a talk therapy that leads to understanding the relationship between thoughts, behaviours and feelings is increasingly identified as the "gold standard" (CAMH 2008). CBT has been shown to be effective for people of all ages and for people of different levels of education and income and various cultural backgrounds. It has also been shown to be effective in either individual or group formats.

If appropriately educated and supported, the family can be a valuable resource for the patient and their MMT physician. The MMT physician can also play a valuable role in encouraging and facilitating access to supports and services, such as relapse prevention programs in the community.

10.5 Community Resources

ConnexOntario Health Services Information exists to improve access to alcohol and drug, gambling and mental health services for the people of Ontario. (See Resource Section)

The Drug and Alcohol Registry of Treatment (DART) provides information about drug and alcohol treatment services in Ontario. (See Resource Section)

ACCS, the Addiction Clinical Consultation Service is designed to serve Health and Social Service professionals including physicians, nurses, psychologists, occupational health staff, social workers, correctional staff, addiction workers and others who care for patients who have alcohol and drug problems. Addiction Clinical Consultation team includes experienced clinicians from medical, psychosocial and pharmacy areas. (See www.camh.net) Contact 1-888-720-ACCS (2227), or (416) 595-6968 in the Toronto area.

11.0 MMT with Concurrent Mental and Physical Disorders

11.1 Overview

MMT physicians need to be skilled in the identification and management of conditions that are common in opioid-dependent patients, such as medical and mental health disorders. All patients should have an identified primary care physician. The MMT physician should encourage the patient to see their primary care physician regularly for ongoing preventive care, screening and chronic disease management.

▶ Standard

S11.1	The MMT physician shall not prescribe methadone for pain without a Health Canada exemption, unless the primary focus of the patient's care is treatment of opioid dependence rather than pain management. In this circumstance, CPSO MMT Program Standards and Guidelines should be followed with appropriate modification for split dosing.

▶ Guidelines

G11.1	The MMT physician should encourage patients to attend a primary care physician or team for ongoing age-appropriate screening and chronic disease management.
G11.2	The MMT physician should have open and regular communication with the patient's primary-care physician.
G11.3	MMT physicians should screen patients for hepatitis C and HIV, and offer referral and treatment when clinically indicated.
G11.4	The MMT physician should assess patients periodically for alcohol use through an alcohol consumption history. Screening questionnaires and laboratory measures might also be considered.
G11.5	For patients with acute pain that warrants short-term opioid therapy, MMT physicians may temporarily split the methadone dose with an additional 10-15 mg evening dose, or prescribe opioids in addition to methadone (See Section 6.8 Split Doses).
G11.6	If opioids are prescribed for acute pain, the MMT physician should choose an opioid that the patient has not misused in the past, and dispense the opioid in small amounts (controlled dispensing). The MMT physician should limit the prescription to the number of days that opioids are typically needed for that particular acute pain condition.
G11.7	The MMT physician should become familiar with the *Canadian Guideline for Safe and Effective Opioid Use in Chronic Non-Cancer Pain* (**http://nationalpaincentre.mcmcaster.ca/opioid/**)
G11.8	The MMT physician may prescribe methadone in split doses for patients with severe chronic pain who require opioids. Usually this should only be done after the patient is on a stable once-daily dose and is receiving 5-6 take-home doses per week.
G11.9	The MMT physician should only attempt long-term opioid therapy for methadone patients with chronic non-cancer pain if: 1) the patient has severe pain from a well-documented diagnosis of a serious nocioceptive or neuropathic condition that would usually require opioid analgesics. Note: *Common conditions such as fibromyaglia or low back pain do not warrant combination methadone and opioid therapy.* 2) the patient has had insufficient analgesic benefit from an adequate trial of non-opioid treatments and from a trial of split methadone dosing.
G11.10	If opioids are prescribed in addition to methadone, the recommended opioids for most patients are codeine and tramadol, followed by morphine. The MMT physician should use strategies to minimize diversion and misuse. The MMT physician should periodically attempt a trial of opioid tapering, particularly in patients on higher opioid doses who continue to report severe pain.
G11.11	The MMT physician should periodically screen and assess MMT patients for anxiety and mood disorders and refer to a mental healthcare professional if they have failed to respond to primary-care treatments.
G11.12	The MMT physician should attempt to decrease long-term benzodiazepine treatment to a lower dose for MMT patients, particularly if they: 1) are on multiple daily doses 2) show signs of misuse 3) are elderly 4) are on a high methadone dose 5) are on other sedating drugs.

11.2 Physical Disorders

11.2.1 Infectious Disease

11.2.1.1 Hepatitis C and HIV

Hepatitis C treatment with interferon and ribavirin can be successfully integrated into MMT. Adherence to anti-retroviral treatment for HIV is higher in patients on MMT than those not receiving MMT (Harris et al. 2010, Uhlmann et al. 2010).

11.2.2 At-Risk Drinking

At-risk drinking and alcohol dependence are common among MMT patients (Backmund et al., 2003, Hillebrand et al. 2001). Excessive alcohol use accelerates liver damage in patients with Hepatitis C (Szabo et al., 2010), although the impact of moderate alcohol consumption is not well understood (Cheung et al., 2010). Alcohol also contributes to substance-induced mood, anxiety and sleep disorders. Alcohol interacts with methadone causing sedation, risk of overdose, aspiration, accidents, violence, and other adverse events.

Methadone treatment does not appear to significantly reduce alcohol consumption in the long-term (Anchersen et al. 2009; Caputo et al. 2002; Srivastava et al. 2008), which suggests that methadone programs do not pay enough attention to the issue. Evidence suggests that counselling about alcohol use is effective in methadone patients (McCusker 2001).

MMT physicians should be aware of special considerations involved in managing alcohol problems, such as:

Low-risk drinking guidelines
The current guidelines recommend no more than 14 standard drinks per week for men and 9 per week for women. Lower limits are recommended for patients with Hepatitis C.

Pharmacotherapy
The first-line medication used to treat alcohol dependence, naltrexone (ReVia ®) is contraindicated in patients on methadone. Available alternatives include disulfiram and acamprosate.

Alcohol withdrawal
To avoid benzodiazepine toxicity, methadone patients in alcohol withdrawal should be given smaller doses of lorazepam (e.g., 1-2 mg) rather than diazepam.

11.2.3 Hepatic, Renal, and Respiratory Disease

Hepatic Disease

- While stable liver dysfunction does not appear to affect methadone levels (Beauverie et al., 2001; Novick et al. 1985), MMT physicians have seen methadone patients who have become very sedated when admitted for acute decompensated cirrhosis. The MMT physician should consider decreasing the dose in this circumstance, and

benzodiazepines should be avoided. The half-life of benzodiazepines can be prolonged in hepatic dysfunction, and benzodiazepines can trigger encephalopathy. The QT interval should be monitored as liver dysfunction is a risk factor for Torsades de Pointes arrhythmias. (Ehret et al. 2006).

Renal Disease

- Evidence suggests that the metabolism of methadone is not affected by renal insufficiency (Kreek et al., 1980, Murtagh et al, 2007)**.** Nonetheless, patients in acute renal failure should be monitored closely for signs of methadone toxicity.

Respiratory Disease

- Tolerance to the respiratory depressant effects of methadone develops very slowly and incompletely. Methadone patients who develop an acute, serious respiratory illness (e.g., pneumonia, COPD exacerbation) should be closely monitored for both worsening respiratory function and methadone toxicity. Abrupt cessation of methadone should be avoided, as withdrawal may cause cardiorespiratory complications due to anxiety and agitation (Friedman et al. 2003; Kienbaum et al. 1998).

Cardiac Disease

- Patients who have cardiomyopathy due to ischemia or other causes are often at higher risk for arrhythmias, therefore their QT interval should be closely monitored and their dose adjusted if necessary. Rapid methadone tapering should be avoided in patients with coronary artery disease as it can trigger cardiorespiratory instability.

11.2.4 Acute Pain

MMT patients are tolerant to the analgesic effects of opioids (Doverty et al., 2001), so if they experience severe acute pain they may require opioids in higher or more frequent doses than non-tolerant patients.

In MMT patients who are eligible for take-home doses and have severe pain unresponsive to non-opioid treatments, temporarily adding an afternoon or evening methadone daily dose (e.g., 10-15 mg) may be helpful. If this is ineffective or not advisable, then the physician might consider a short-term opioid prescription. MMT patients' views on opioid use should be discussed before prescribing; some MMT patients are concerned that opioids will trigger a relapse and would prefer non-opioid analgesics. If possible, the MMT physician should avoid the MMT patient's previous opioid of abuse or an opioid commonly abused in the community. For most MMT patients, morphine is preferred over oxycodone or hydromorphone.

11.2.5 Chronic Non-Cancer Pain

Chronic non-cancer pain is common in MMT patients (Rosenblum et al., 2003). MMT physicians who prescribe methadone are encouraged to become familiar with the *Canadian Guideline for Safe and Effective Opioid Use in Chronic Non-Cancer Pain* (http://nationalpaincentre.mcmaster.ca/opioid/). However MMTpatients with CNCP present clinical challenges that require special consideration when prescribing opioids.

Table 12: Overview of Pain Management

Pain Condition	Management
Mild to moderate Common conditions such as fibromyalgia, low back pain.	Non-opioid treatments
Severe nocioceptive or neuropathic pain condition that usually requires opioid therapy.	First-line: Non-opioid treatments Second-line: Split methadone dose Third-line: Codeine or tramadol Fourth-line: Potent opioids e.g., morphine.

11.2.5.1 Methadone for Analgesia

MMT physicians cannot prescribe methadone as an analgesic for non-addicted patients with chronic pain, unless they have a special exemption from Health Canada. This exemption is independent of the exemption for methadone as a treatment of addiction.

MMT physicians with the Health Canada addiction exemption can prescribe methadone both as an analgesic and as an opioid substitution therapy for patients who have concurrent addiction and acute pain. However for chronic pain management, where, over time, the treatment of pain, rather than that of opioid dependence, becomes the primary focus of the patient's care, the MMT physician requires an exemption to prescribe methadone for pain and the patient should be taken off from the CPSO MMT Patient Registry for opioid dependence.

Controlled trials have found that methadone is of comparable effectiveness to morphine as an analgesic (Bruera et al. 2004; Mercadante et al. 2008). While the duration of analgesic action of methadone is no more than eight hours (Grochow et al., 1989), an initial trial of once daily dosing is suggested. Patients with concurrent pain and opioid addiction often experience substantial pain relief once methadone treatment is initiated. When an optimal dose is reached, the dose may be split if the patient continues to experience severe pain unrelated to withdrawal several hours after the morning dose. Patients should be eligible for 5-6 take-home doses before receiving a split dose. Consultation with a physician experienced in methadone and pain should be considered.

11.2.5.2 Opioids in Combination with Methadone

Research to date has not examined the safety or effectiveness of methadone in combination with other opioids for opioid-dependent patients with chronic non-cancer pain. Furthermore, long-term opioid prescribing in MMT patients makes it difficult to prevent and detect opioid misuse and diversion. Therefore opioids should only be used if there is strong likelihood of benefit, (i.e. patients with serious, well-defined nociceptive or neuropathic conditions who have not responded to first-line non-opioid treatments or to split methadone dosing). Use of opioids is not justified in MMT patients with common pain conditions such as fibromyalgia or low back pain.

If split methadone doses are ineffective, then codeine or tramadol can be tried. If more potent opioids are required, in many cases the MMT physician should consider using

morphine rather than oxycodone or hydromorphone (Rauck et al. 2007). Evidence suggests that oxycodone and hydromorphone have a higher risk of addiction and overdose than morphine, and therefore the latter is preferred in high risk patients. Oxycodone is a common drug of abuse in Ontario, and it is the most common opioid involved in fatal opioid overdoses (Dhalla et al, 2009). See *Canadian Guideline for the Safe and Effective Opioid Use in Chronic Non-Cancer Pain.* http://nationalpaincentre.mcmaster.ca/opioid/).

11.2.5.3 Preventing Misuse and Diversion in Patients on both Methadone and Opioids

MMT patients do not always inform their MMT physician if they are receiving opioids from another physician. Collaboration and communication between the MMT physician and pharmacist can enhance knowledge of other medications the MMT patient may be taking. For some MMT patients, ongoing UDS provides appropriate structure while on regularly prescribed opioids. Until the prescription opioid monitoring system is in place, MMT physicians have few options other than to:

- insist on communicating with the patient's non-MMT physicians
- obtain records from emergency department visits and hospitalization
- advise non-MMT physicians to order UDS for methadone when prescribing opioids, particularly if they do not know the patient well or if the patient is at high risk for opioid misuse.

If the MMT physician knows that another physician is prescribing opioids for the patient, several strategies can be implemented to minimize opioid diversion and misuse. The opioid can be dispensed along with the methadone take-home doses. Pill counts and regular urine drug screening can also be helpful. Close communication with the patient's opioid prescriber is advised to prevent dangerous drug combinations.

11.5.3.3 Opioid Tapering

Tapering is indicated for patients who report severe pain and pain-related disability despite reasonable opioid doses. Research has demonstrated that these patients experience reduced pain and improved mood and functioning with opioid tapering (Baron et al. 2006, Crisostomo et al. 2008, Hooten et al. 2007)**.**

11.3 Mental Illness

11.3.1 Anxiety and Mood Disorders

The prevalence of anxiety and mood disorders is several times higher in MMT patients than in the general population (Callaly et al. 2001; Mason et al. 1998). Co-occurrence of substance abuse and psychiatric problems is frequently diagnosed in patients in MMT, particularly Axis I and Axis II disorders and depressed MMT patients can be more sensitive to opioid withdrawal (Astals et al. 2008; Cacciola et al. 2001; Callaly et al. 2001; Elkader et al. 2009). To date there is little evidence to support the use of antidepressants in treating mood disorders in MMT patients (Carpenter et al. 2004; Dean et al. 2002). Therefore MMT physicians might consider referring MMT patients for more intensive assessment and

treatment if they have persistent depression and anxiety despite an initial trial of pharmacotherapy.

11.4 Benzodiazepines

Benzodiazepine use in MMT patients is associated with increased psychological distress, risk for overdose, higher risk of suicidal behaviour, violence, impaired attention and memory, impaired driving and risk for continuing poly-drug use (Bleich et al. 2002; Brands et al. 2008; Caplehorn & Drummer, 2002; Darke et al. 2010; Darke et al. 2009; DeMaria et al. 2000; Man Lan-Ho et al. 2004) Furthermore inconsistent results regarding the impact of benzodiazepine use on treatment retention have been reported; negative impact (Peles et al. 2010) or no impact on treatment retention (Kellogg et al. 2006). As well, an observational study documented reduced symptoms of depression in MMT patients who were tapered off benzodiazepines and started on antidepressant therapy (Schreiber et al. 2008).

WHO Guidelines (2009) suggest that gradual withdrawal from benzodiazepines may be necessary for benzodiazepine users in MMT programs.

12.0 Methadone Toxicity

12.1 Overview

Methadone toxicity presents a serious challenge to MMT physicians.

Opioid toxicity leading to overdose is characterized by a decreased level of consciousness, respiratory depression and pinpoint pupils. Two features of methadone toxicity make interpretation of these signs difficult:

1. Definite signs of methadone toxicity may not become apparent for 5-9 hours after the overdose (Caplehorn and Drummer 2002; Lovecchio et al. 2007).
2. MMT patients who have had an overdose may appear relatively alert during conversation, succumbing to respiratory depression during sleep (Caplehorn 1999).

►Standard

None for this section.

►Guidelines

G12.1	The MMT physician should assess patients in person or refer them to the emergency department if they might have taken a dose above and beyond what would be considered a safe dose, given their underlying tolerance, concurrent medication use, and health status.
G12.2	If, after assessment, the MMT physician is concerned that the patient is at imminent risk for methadone toxicity, the MMT physician should take the following steps: ▪ explain the risks of methadone overdose, including respiratory depression and death, and advise the patient that an ambulance is being called ▪ ensure a staff member keeps the patient awake until the ambulance arrives ▪ arrange an involuntary mental health assessment if the patient refuses to attend the emergency department

12.2 Dosing and Assessment for Possible Methadone Toxicity

Definition of a toxic dose

Reasonable dose increases usually range between 10-15 mg every 3-5 days (See Section 6.5 Table 06). For example, if a patient has consistently been on 50 mg/day for several weeks and then receives 65 mg by mistake, this would be considered within the range of a "reasonable" dose increase for that patient. However, if the patient was just initiated on 30 mg the day before and then receives 45 mg on the second day, they could be at risk of methadone toxicity.

If the exact amount ingested is not known with certainty, it is safest to manage the patient as if they took an overdose, even if the patient reports that he/she is alert and only took a "small amount".

The risk of toxicity is determined not just by the amount of the extra dose but by the patient's underlying tolerance and underlying health status. Even 'small'extra doses of 15-20 mg can cause toxicity during the first two weeks of methadone titration, or if the patient is elderly or has a respiratory illness. See Table 03, Section 6.1 and 6.3.

Assessment of the MMT patient who may have taken a toxic dose

If the patient is currently at the clinic, the MMT physician should engage the patient in conversation for at least five minutes, as an overdosed patient will have trouble maintaining alertness for more than a few minutes. During the conversation, observe for sweating, emotional lability, slurred or drawling speech, and "nodding off". If possible, the patient should also be observed when not engaged in conversation. Falling asleep, 'dozing' or 'napping' could indicate toxicity even if the patient is easily rousable. Remember that the peak effect of the methadone is apparent several hours after ingestion (Wolff 2002).

If the patient is at home, ask family members to describe the patient's sleep. Loud snoring and apneic episodes during sleep could indicate a life-threatening overdose.

12.3 Patient Referral to the Emergency Department for Overdose

The information sheet in Appendix I(v) should be completed, and given to the paramedics or faxed to the emergency department. If possible, the MMT physician should speak directly with the attending emergency department physician or nurse, advising them that:

1. the patient should be observed for a minimum of 10 hours.
2. the patient should be discharged only if they have not displayed any signs of lethargy or sedation during that time.

If the MMT physician decides not to call the ambulance, a reliable adult should accompany the patient to the emergency department. The person must understand the life-threatening nature of the overdose and the dangers of refusing emergency department management.

If the MMT physician is uncertain about appropriate management, contact the Ontario Poison Centre.
http://www.ontariopoisoncentre.com/poisoncentre/
or call 1-800-268-9017 or (416) 813-5900

12.4 Refusal to go to Emergency Department

If the patient refuses to go the emergency department, then it is appropriate to fill out a Form 1, which allows an involuntary assessment of the patient. Many MMT physicians are reluctant to complete a Form 1 on a patient who is alert and coherent. However, methadone overdose meets the requirements for a Form 1 because:

1) The patient is at imminent risk of bodily harm.
2) The patient has a mental health diagnosis (addiction) that makes it difficult for them to appreciate the need for medical treatment. (Clinical experience suggests methadone patients tend to be far more concerned about methadone withdrawal than intoxication. The MMT patient might be worried that they will receive naloxone in the ED or that their next methadone dose will be reduced or delayed.)

If the patient refuses to go to the emergency department and a clinical decision is made to not complete a Form 1 (e.g., no MMT physician available onsite or the MMT physician is speaking to the patient by phone and have not assessed the patient in the preceding week as required by a Form 1), then it is reasonable to send an ambulance or police to the patient's home.

If the MMT physician decides not to complete a Form 1 or to call emergency services, then the patient should be asked to sign an "AMA or Against Medical Advice" form (if the patient is in the clinic). Explain to the patient and their partner or family member if available that the patient is at risk of respiratory depression and death, especially if they fall asleep. Advise the patient not to use any other substances or medications.

13.0 MMT Considerations during Pregnancy

13.1 Overview

Pregnant opioid-dependent women are at increased risk of obstetrical and medical complications due to repeated cycles of opioid intoxication and withdrawal. Pregnant opioid-dependent women have higher rates of premature delivery and infants with low birth weight leading to higher rates of infant morbidity and mortality (Finnegan 1978; Hulse et al. 1997, 1998; Kandall et al. 1977; Little et al. 1990; Rementeria and Nunag 1973; Stern 1966; Stimmel et al. 1982; Vucinovic et al. 2008; Wilson et al. 1981). Morbidity and mortality have been attributed to the direct effect of the drug itself, but are also secondary to other associated lifestyle factors such as poor nutrition, inadequate prenatal care attendance and concomitant substance use such as alcohol and tobacco (Fricker and Segal 1978, Hulse et al. 1997, Vucinovic et al. 2008).

The benefits of MMT during pregnancy include improved prenatal care, nutritional status and social stability leading to increased likelihood of maternal custody, as well as, reduced incidence of pre-term delivery, low birth weight and infant mortality (Chang et al. 1992; Kaltenback and Finnegan 1992; Wilson et al. 1981).

►Standard

S13.1	The MMT physician shall offer MMT to opioid-dependant pregnant patients on an urgent basis.

►Guidelines

G13.1	MMT physicians should ensure pregnant opioid-dependent patients are counselled regarding the risks and benefits of MMT during pregnancy.
G13.2	The MMT physician should consider inpatient initiation during pregnancy in order to monitor for withdrawal severity and fetal distress.
G13.3	The MMT physician should aim for a maintenance dose of methadone that keeps the patient comfortable for 24 hours and helps maintain abstinence.
G13.4	MMT physicians should consider split dosing during pregnancy as an alternative strategy to increasing the methadone dose in the third trimester.
G13.5	The MMT physician should assess the MMT dose for adjustments, especially for dose increases during the third trimester of pregnancy to prevent maternal withdrawal symptoms.
G13.6	The MMT physician should consider dose replacement after reported emesis in pregnant women.
G13.7	The MMT physician should consider tapering and detoxification in selected patients based on clinical and social stability, previous good response to tapering, and no concurrent psychiatric disorders or addiction to other substances.
G13.8	The MMT physician should assist the MMT patient in obtaining adequate prenatal care by referring for obstetrical care as soon as pregnancy is identified.
G13.9	The MMT physician should ensure there is open communication between the methadone and obstetrical physician regarding the use of MMT during pregnancy and planning for labour and delivery.
G13.10	During labour and delivery the MMT physician should ensure the pregnant MMT patient receives her regular daily methadone dose.

G13.11	The MMT physician should monitor the MMT patient closely for symptoms of methadone intoxication and mood disorders during the postpartum period.
G13.12	The MMT physician may need additional visits with the patient during the immediate postpartum period to provide support during this transition phase.
G13.13	The MMT physician should encourage breastfeeding during MMT.
G13.14	The MMT physician should consider referring to a child protection agency, depending on the mother's length of time in treatment, the stability of substance use, and social situation.

13.2 Effects of Methadone during Pregnancy

Methadone crosses the placenta, but has not been found to be teratogenic. There is weak evidence linking strabismus to opioid use during pregnancy, especially with methadone exposure in utero (Gill et al. 2003; Nelson et al. 1987)**.**

To date, no conclusive long-term study has been published about the long-term effects of neonatal exposure to methadone (Chasnoff et al. 1982; Hans 1989; Hunt et al. 2008; Kaltenbach and Finnegan 1987; Lifschitz et al. 1985). Environmental factors and caregivers can play a significant role in mediating these effects of methadone exposure on infants' growth and development.

The most significant risk of methadone exposure during pregnancy is neonatal withdrawal also known as neonatal abstinence syndrome (NAS) (Kaltenbach & Finnegan 1986)**.** Up to 85% of newborns exposed to methadone experience withdrawal symptoms and signs (Bell and Lau 1995; Finnegan et al. 1975) such as:

1) central nervous system (CNS) hyperirritability (high-pitched cry, increased muscle tone, sleep disturbances, tremors, seizures)
2) gastrointestinal dysfunction (poor feeding, regurgitation, vomiting, loose stools)
3) metabolic, vasomotor, and respiratory disturbances (sweating, recurrent sneezing, yawning, fever).

Withdrawal usually begins within 72 hours of birth, but late presentations (up to 2-4 weeks after birth) have been reported (Finnegan amd Kaltenbach 1992) and symptoms may last for several weeks or months.

13.3 MMT during Pregnancy

13.3.1 Inpatient vs Outpatient

See Appendix L: Protocols for MMT and Pregnancy.

There are no studies to demonstrate the efficacy and safety of inpatient over outpatient stabilization. However, inpatient stays allow for investigations of maternal health and prenatal status and referral to others (e.g., social worker, obstetrical care provider).

Inpatient initiation is not always feasible due to personal factors (e.g., fear of medical personnel and hospitals, child care issues and lack of support from family or partner) or

systemic factors (e.g., unavailability of methadone in the hospital and limited staff experience). However, if a pregnant woman complains of uterine irritability (e.g., abdominal cramping and bleeding) during outpatient initiation, hospital admission is indicated.

13.3.2 Methadone Dosing During Pregnancy

13.3.2.1 Establishing a Maintenance Dose

An appropriate maintenance dose should be determined for each individual. A clear relationship between maternal methadone dose and the severity of Neonatal Abstinence Syndrome (NAS) has not been established (Berghella et al. 2003; Dashe et al. 2002; Doberczak et al. 1993; Kaltenbach and Comfort 1997) due to the potential effect of other factors such as concomitant drug use (e.g. cocaine, benzodiazepines) on neonatal withdrawal (Berghella et al. 2003; Mayes and Carroll 1996). The risks of illicit opioid use outweigh the potential risks of higher methadone doses.

13.3.2.2 Dose Splitting During Pregnancy

Twice-daily methadone dosing has been associated with sustained plasma methadone levels and fewer withdrawal symptoms resulting in improved treatment compliance and decreased use of other illicit substances (Swift et al. 1989, Wittmann and Segal 1991). Split doses have also been shown to cause less suppression of fetal behaviour than with single daily dosing which has demonstrated decreases in both fetal movements and fetal breathing after dosing (Jansson et al. 2009; Wittmann and Segal 1991). Therefore, when pregnant women continue to experience withdrawal symptoms with single daily dosing, split dosing (i.e., every 12 hours) can be considered. Women need to meet stability criteria (See Section 8.3 Take Home Dose Criteria) for take-home doses or arrangements can be made with the pharmacy to provide an evening observed dose.

13.3.2.3 Dose Adjustments During Pregnancy

Women in MMT prior to conception can continue on their pre-pregnancy dose during the first and second trimesters (Finnegan 1991). Methadone clearance rates gradually increases from the first to the third trimester resulting in lower mean serum methadone levels as the pregnancy progresses (Drozdick et al. 2002; Jarvis et al. 1999; Wolff et al. 2005). This change in methadone clearance has been attributed to different factors such as increased methadone metabolism during pregnancy, increased maternal renal elimination, increased volume of distribution and tissue binding, and additional metabolism by placenta and fetus (Pond et al. 1985, Swift et al. 1989). Small increments in methadone dose later in pregnancy will be required.

13.3.2.4 Managing Vomited Doses

See Section 6.10 Vomited Doses.

13.4 MMT Tapering or Withdrawal during Pregnancy

Recent clinical experience with MMT detoxification (i.e., methadone-assisted withdrawal) has not demonstrated any increased incidence of obstetrical complications or adverse neonatal outcomes during the first, second or third trimesters (Blinick et al. 1969; Dashe et al. 1998; Jones et al. 2008; Luty et al. 2003; Maas et al. 1990). However, MMT detoxification has been associated with clinical instability and a high risk of relapse to substance use requiring resumption of MMT.

There is limited guidance in terms of the rate of methadone tapering or detoxification. Some studies have proposed reducing the dose by 1-2 mg/day as an inpatient or by 2-10 mg every 1-2 weeks as an outpatient (Archie 1998; Finnegan 1991; Jarvis and Schnoll 1994; Kandall et al. 1999). However, these numbers are not based on systematic studies. In pregnancy, the dose should be decreased slowly by 5-10% per week. This process should be stopped if the pregnant woman reports any adverse outcomes such as relapse to drug use, increased cravings, intolerable withdrawal symptoms or obstetrical complications.

Motivated women who have a short addiction history, are medically and socially stable with a good support network and have no concurrent psychiatric disorder may have better outcomes following detoxification.

13.5 Prenatal Care for MMT Pregnant Patients

The addition of on-site prenatal care has been shown to improve attendance and pregnancy outcomes (Chang et al. 1992). Binder & Vavrinkova showed that methadone substitution treatment provides pregnant women with greater social stabilization and prenatal care (Binder and Vavrinkova 2008). Therefore, comprehensive care which provides MMT and prenatal care is the most effective approach in increasing patient retention and reducing adverse neonatal outcomes (Ellwood et al. 1987).

13.6 Intrapartum Management for MMT Pregnant Patients

Methadone will not provide pain relief during labour and additional analgesia will be required.

13.7 Postpartum Management for MMT Patients

13.7.1 Dosing

A few days or weeks postpartum, the MMT patient may find her established dose of methadone is too high. If so, it should be decreased by 5-10 mg every week based on clinical symptoms until a new stable dose is reached. The MMT physician should consider the risk of relapse to illicit opioids prior to beginning the decrease.

13.7.2 Support

Mothers often feel extremely guilty if the infant exhibits symptoms of opioid withdrawal requiring treatment and an extended hospital stay. The services of public health nurses and

attendance at drop-in centers and parenting classes (e.g., Ontario Early Years Centers) should be encouraged.

13.7.3 Breastfeeding

Methadone enters the breast milk in very small amounts that are unlikely to be clinically significant (Glatstein et al. 2008; Jansson et al. 2004)**.** The mean daily amount of methadone ingested by infants ranges between 0.01 and 0.05 mg depending on the maternal methadone dose. This amount is not sufficient to prevent neonatal absence syndrome (NAS) and the infant still requires additional opioid treatment for NAS.

13.7.3.1 Breastfeeding and Hepatitis C

No studies have demonstrated transmission of HCV through breast milk alone to infants (Wong and Lee, 2006)**.** Breastfeeding by women who are infected with hepatitis C (HCV) is considered safe.

13.8 Reporting to Child Protection Agencies

In Ontario, the Child and Family Services Act outlines a legal responsibility to promote the well-being and protection of children. Any health care professional who has reasonable grounds to suspect that a child is, or may be, in need of protection has a legal duty to report this suspicion. In Canada, the fetus is not legally recognized as a person and as such, the obligation to report only applies once the child is born. Prenatally, health care providers may contact child protection services after discussion and with consent from the pregnant woman. Patients should be encouraged to self-report during the prenatal period in order to increase self-efficacy, dignity and stability while promoting an open and informed decision-making by child protection authorities. Consider immediate referral if the pregnant woman has children in her care and there is a child protection concern.

14.0 MMT in Federal/Provincial Correctional Facilities

14.1 Overview

MMT in correctional facilities is unique and provides good quality care that meets a standard. The controlled environment, imperatives for security, and the governance of correctional policy may affect the institutional MMT physician's ability to provide patient-centered care at community standards. The trusting therapeutic relationship between MMT physicians and patients must remain the focus of treatment.

High risk behaviour such as injection opioid use can be seen within correctional facilities. The prevalence of HIV and viral hepatitis is high in the correctional population due in part to the prevalence of needle sharing.

Incarcerated opioid-dependent individuals should be offered ongoing MMT or initiation of MMT.

►Standards

S14.1	The institutional MMT physician shall ensure a Treatment Agreement is signed by the patient.
S14.2	The institutional MMT physician shall ensure the Treatment Agreement and medical history is kept as part of the medical file.
S14.3	The institutional MMT physician shall ensure healthcare staff contacts the previous MMT physician and/or pharmacy to determine the patient's current dose, the date/time of the last dose received to ensure that three or more doses were not missed.
S14.4	The institutional MMT physician shall ensure that protocols to treat a known or suspected opioid overdose are available to all health care staff. NARCAN® must be available.
S14.5	The institutional MMT physician shall ensure arrangements are made for methadone pick-up at a community pharmacy in the event of an outside pass.
S14.6	The institutional MMT physician shall make every attempt to educate the patient of potential for relapse and the dangers of overdose, and encourage adherence to treatment.
S14.7	The institutional MMT physician shall not prescribe take-home doses to a patient upon release from the correctional facility.

►Guidelines

G14.1	The institutional MMT physician should ensure program rules and expectations are in writing and verbally described to each patient.
G14.2	The institutional MMT physician should ensure dispensing times are clearly defined.
G14.3	The institutional MMT physician should clearly describe the expectations regarding provision of UDS samples, appointments with the MMT physician, and general behaviour at the onset of treatment.
G14.4	The institutional MMT physician should ensure UDS results are maintained in the medical chart.
G14.5	The institutional MMT physician should ensure UDS results are not shared with non-medical staff except when there is a safety issue and that if shared should not be used for punitive purposes.
G14.6	The institutional MMT physician should ensure UDS are performed at intake and periodically thereafter, particularly if the patient shows evidence of intoxication, injection drug use or diversion of methadone.
G14.7	The institutional MMT physician should assess patients in person or via telemedicine for dose increases.
G14.8	In exceptional circumstances due to facility constraints, (e.g. lockdown or inmate movement issues) when the institutional MMT physician cannot assess a patient, the institutional MMT physician should designate a nurse to assess the patient for dose increases. A single dose increase of no more than 10 mg can be given by the nurse prior to the assessment of the facility physician.
G14.9	The institutional MMT physician should ensure a process is in place for the safe administration of methadone for patients.
G14.10	The institutional MMT physician should ensure a safe process is in place to initiate patients on MMT, if feasible.
G14.11	The institutional MMT physician should ensure every effort is made to provide continuity of care with a community physician.
G14.12	Prior to release from the facility, the institutional MMT physician should slowly decrease (taper) the methadone dose if the patient is going to a community with no available MMT physician. This should be done only as a last resort.
G14.13	The institutional MMT physician should ensure a bridging prescription is faxed to a community pharmacy until the patient's next appointment if there is a gap of time from the date of release to the scheduled appointment with the community MMT physician. Details of the prescription should be communicated with the community MMT physician.
G14.14	The institutional MMT physician should ensure counselling and support is provided throughout the involuntary taper process and that the opportunity for the patient to reapply for MMT is available if they can adhere to program requirements.

14.2 Approaches to Treatment in a Correctional Facility

14.2.1 Approach to Treatment

It must be clear that the interests of the patient are the priority of the institutional MMT physician. A multidisciplinary team approach to the provision of MMT is essential in this

setting and should include clinical staff, substance abuse counselors (where available), and persons responsible for the patients MMT in the community.

Confidentiality is extremely important in the correctional system, as in all medical interactions. Conflicts are often avoidable when the structure of the treatment is conveyed to both patients and staff.

14.2.2 UDS

It is essential that urine toxicology screening results used in MMT correctional facilities is for therapeutic purposes and results should be maintained in the medical chart.

14.2.3 Missed or Vomited Doses

Correctional facilities may have specific procedures in place to handle missed or vomited doses.

14.3 Continuing Ongoing MMT

11.3.1 Issues Unique to Providing MMT in Correctional Facilities

14.3.1.1 Methadone Brought With a Patient

Methadone accompanying any patient should be discarded unless continuity of handling can be proven, such as in a transfer from another correctional facility. (See Correctional policies for the discarding of narcotics).

14.3.1.2 Treatment Agreement

The institutional MMT physician shall ensure a treatment agreement is signed by the patient and ensure that the treatment agreement and medical history are kept as part of the medical file.

14.3.1.3 Dosing on Admission

Confirmation must be obtained about whether a patient is enrolled in and attending a community MMT program upon admission to the correctional facility and prior to dispensing the first methadone dose.

Often institutional MMT physicians are not available on the weekend to maintain patients on MMT if incarceration occurs after hours, leaving patients at risk for destabilization. For patients who mostly have observed ingestion at the pharmacy with less than or equal to three carries per week, a nurse may assess the patient (vitals signs, appearance and level of alertness, symptoms of withdrawal and intoxication and presence of EDDP in their urine) to allow MMT to continue at the same dose. The institutional MMT physician may then fax a methadone prescription to the pharmacy at the correctional facility for the same dose or a lower dose. Alternatively the patient's community MMT physician may provide a prescription for a bridging dose until the institutional MMT is available.

In order to provide safe MMT, institutional MMT physicians must use their clinical judgment to determine the appropriate dose (e.g., 50% of the stated dose if diversion of take-home doses is suspected, or of a high maintenance dose, e.g., the dose is greater than or equal to 150 mg). If the dose is reduced, the institutional MMT physician should re-assess the patient frequently for symptoms of withdrawal and intoxication, and appropriate dose changes should be made. Benzodiazepines, or sedating sleep aids should be used cautiously if at all until the institutional MMT physician has done an appropriate assessment of the patient. If the patient appears intoxicated from the nurse's assessment, in these circumstances, the patient should be assessed within a reasonable amount of time to avoid further discomfort of withdrawal. The Opioid Detoxification Protocol should be followed.

See Section 6.9 Table 08 for protocols on management of missed doses. For patients with "take-home privileges", the physician may wish to verify recent ingestion of methadone by testing for evidence of EDDP in their urine.

14.3.1.4 Dose Increases

In exceptional circumstances due to facility constraints, (e.g., lockdown or offender movement issues) when the institutional MMT physician cannot assess an inmate, the institutional MMT physician should designate a nurse to assess a patient for dose increases. A single dose increase of no more than 10 mg can be given by the nurse prior to the assessment of the institutional/MMT physician.

The nurse's assessment is documented in the chart and includes the following:

1) The reason why the assessment is being performed by the R.N. and not the physician
2) Any obvious signs of withdrawal noted by the R.N.
3) When the withdrawal symptoms begin in relation to the dose (i.e., 8 hours before the next dose, or 16 hours after the dose)
4) Time of use
5) Drug cravings
6) Time and amount of last dose
7) Mental status
8) Sign and symptoms of sedation
9) Any ongoing opioid use (drug name, amount used, and route of use).

14.4 Observed Administration

It is not uncommon for MMT patients to be under considerable pressure from other patients to divert their medication. Adequate steps to avoid diversion are critical to ensure MMT patients safety within the facility.

Below are suggested recommendations that can be incorporated into the facilities administration process:

- MMT patients to show proper identification.
- MMT patients receiving methadone should be isolated from other patients during administration process.
- Drink water following administration.
- Nurse can inspect mouth before and/or after.
- No wearing of bulky clothing (i.e., parkas, hoodies)
- No bringing cups or containers into the administration area.
- Frisking MMT patients before entering and/or upon leaving administration area.
- Limit access to water post ingestion (fountains, bathrooms).
- A 20 minute direct observation should follow immediately.

14.5 Initiating MMT in a Correctional Facility

If a patient is not receiving methadone at the time of incarceration, the following conditions should be met:

1) The patient must meet or have met in the past the DSM-IV diagnostic criteria for opioid substance dependence.
2) A UDS must be interpreted and a complete assessment performed prior to initiation.
3) The usual reporting procedure to the CPSO must be followed.
4) Patients not currently using opioids, but where their documented history clearly shows a pattern of long-term opioid dependence continuing until the time of incarceration, should be considered for initiation on methadone while in the correctional facility. (See Section 5.3.4.1)
5) Pregnant patients currently using opioids must be offered MMT while incarcerated. Patients with HIV infection, or hepatitis B or C should be made a high priority for being offered methadone treatment while incarcerated.

14.6 Accidental Overdose of Methadone

Patients should be transported to a community hospital emergency department for assessment and observation. If returned to the institution, a procedure for close observation for at least 24 hours should be in place. Naloxone (Narcan®) must be available in all correctional facility health centers.

14.7 Out-of-Facility Pass

The institutional MMT physician shall ensure that arrangements are made for methadone pick-up at a community pharmacy in the event of an outside pass.

14.8 Treatment Planning for Release

It is imperative that every attempt to provide good discharge planning is done prior to release. Patients are at highest risk of overdose after release from a correctional facility if an appropriate release plan is not made. However, release dates are not always known and patients may be unexpectedly released precipitously and/or directly from court.

14.8.1 Treatment Planning—Release Date Known

When the release date of the patient is known arrangements should be made in advance. An appointment should be scheduled with the community MMT physician and appropriate clinical information should be sent.

14.8.2 Treatment planning - Release Date Unknown or Unexpected

Patients are often released from custody directly from Court or on very short notice without the knowledge of the facility healthcare staff. Therefore where possible:

1. Patients should receive their daily dose of Methadone prior to leaving the facility.
2. Patients should be further advised to contact the facility healthcare staff if they are released directly from court without the benefit of a release plan.

If a patient is released without a community MMT physician, every effort should be made to find one for the patient by contacting the Methadone Program at the CPSO.

If assistance is required by the facility in finding a local pharmacy that dispenses methadone, contact the Ontario College of Pharmacists.

14.9 Take-Home Doses

The institutional MMT physician shall not prescribe take-home doses to a patient upon release from the correctional facility.

14.10 Involuntary Withdrawal

See Section 9.3.

15. Hospital-Based MMT

Attending Physician (or Most Responsible Physician [MRP]): the physician who is responsible for the overall care of the patient, and who must approve all orders written by other physicians.

Hospital MMT Physician: the physician who prescribes methadone. This is usually a different physician than the MRP. For example, when a patient on a stable dose of methadone is admitted to the hospital with pneumonia, the attending physician will manage the pneumonia and the hospital MMT physician will order the methadone.

15.1 Overview

Physicians without a methadone exemption are not allowed to order or prescribe methadone unless they receive a special exemption from Health Canada. Temporary exemptions are only valid for one specific patient, and only for the duration of that patient's stay in hospital. Exemptions can be obtained by calling Health Canada, Office of Controlled Substances.

In many cases, hospital physicians know little about MMT and must rely on the expertise of an MMT physician. General or psychiatric hospitals should identify at least one methadone physician, on staff or in the community, who has agreed to be available for telephone consultations. If feasible, the community methadone physician should seek out active hospital privileges so that he or she may write hospital orders for methadone.

►Standard

None for this section.

►Guidelines

G15.1	General hospitals should have at least one MMT physician who is on their medical staff and available for consultation. Methadone should be on the hospital formulary.
G15.2	The hospital MMT physician should verify the patient's current dose and date it was last dispensed with the patient's pharmacy.
G15.3	The hospital MMT physician should ensure the prescription at the community pharmacy is cancelled for the duration of the patient's hospital stay.
G15.4	The hospital MMT physician should conduct a focused assessment with these objectives: 1. Identify acute risk factors for methadone toxicity. 2. Obtain a history of methadone use. 3. Order a UDS if clinically unstable. 4. Order an ECG if patient is on a high dose or has risk factors for arrhythmias.
G15.5	The hospital methadone order should specify that the dose is to be mixed in orange juice, and dispensed daily under the observation of a nurse. The order should also specify dispensing dates, and should direct nurses to withhold the dose if the patient shows signs of sedation or intoxication.
G15.6	If the patient is n.p.o., the hospital MMT physician may allow the methadone to be mixed in water (or clear juice, with the attending physician's approval).
G15.7	The hospital MMT physician should prescribe oral or parenteral opioids to minimize withdrawal symptoms if methadone is not available or is contraindicated (e.g. prolonged QT interval).
G15.8	To avoid methadone toxicity, the hospital MMT physician should monitor for the emergence of risk factors during the patient's hospital stay, such as co-prescribing of sedating drugs. The methadone dose should be adjusted accordingly.
G15.9	On discharge, the hospital MMT physician may write a prescription for the patient's community pharmacy to last for several days until the patient can see their community MMT physician. A hospital prescription may not be necessary if the patient has take-home doses at home (at the same dose as that provided in hospital).
G15.10	MMT may be initiated in-hospital for pregnant patients, and for patients requiring prolonged hospitalization, who might leave if their acute opioid-withdrawal symptoms are not treated.

15.2 Guidelines for Hospital Pharmacies and Medical Administrators

All hospitals are encouraged to have methadone on their formulary. If methadone is not on the formulary, the patient may bring their take-home doses if available, or a community pharmacy may deliver methadone to the hospital. A take-home bottle should only be used if it is properly labeled and unopened. Methadone should be stored in a locked narcotic cupboard and dispensed under the supervision of a nurse.

15.3 MMT Physicians Working in a Hospital

15.3.1 Verifying the Community Dose

It is not safe to rely solely on the patient's history or the community MMT physician's office for verification of the dose. Only the dispensing pharmacist is able to verify with certainty whether the patient has filled their methadone prescription. If the pharmacy is closed and the dose cannot be verified, a safe dose (e.g., 20-30 mg) can be given to ameliorate withdrawal symptoms. If feasible, the urine should be tested to confirm that the patient has recently taken methadone. The hospital MMT physician should cancel the methadone prescription for the community pharmacy for the anticipated duration of the hospital stay.

15.3.2 In-Hospital Assessment of the Patient

A focused assessment will identify acute risk factors for methadone toxicity. The following should be included in the assessment:

History:

- Methadone dose, recent changes in dose, missed doses, number of take-home doses per week, and exact date and time of the last dose.
- Recent alcohol and substance use.

Chart review:

- Reason for hospital admission
- Out-patient and in-hospital medications
- Cardiorespiratory, hepatic and renal status.

Investigations:

- Baseline UDS
- ECG if on dose above 120 mg or risk factors for QT prolongation, e.g., electrolyte disturbances.

15.3.3 Hospital Methadone Order

The order should be similar to community prescriptions, specifying that the dose is to be mixed in juice and ingestion is to be observed by a nurse. Start and end dates should be specified in the order and nurses should be instructed to hold the dose if the patient shows signs of sedation or intoxication.

15.3.4 Patients on "Nothing by Mouth" (n.p.o)

If the patient is unable to take oral medications or fluids, withdrawal can be lessened with scheduled doses of parental morphine or hydromorphone. If possible, peripheral and central lines should be avoided in patients who have recently been using injection drugs.

15.3.5 Adjusting the Dose

There have been case reports of serious toxicity in hospitalized patients on methadone, caused by drug interactions or the patient's medical condition. Close monitoring is required if the patient has:

1) medications introduced that are sedating or that inhibit methadone metabolism (See Appendix B)
2) a decreased level of consciousness
3) an acute cardiorespiratory illness
4) missed methadone doses prior to hospitalization
5) has worsening hepatic or renal function.

In these circumstances, frequent observation should be ordered, specifying that the dose is to be withheld if the patient shows signs of sedation or intoxication.

When adjusting the dose the hospital MMT physician should keep in mind that acute methadone withdrawal can have serious medical consequences in patients with medical illness. Even intubated patients in a coma will undergo withdrawal if MMT is abruptly discontinued which can cause agitation and cardiorespiratory instability (Friedman et al. 2003; Kienbaum et al. 1998)**.** Therefore methadone should not be rapidly tapered or discontinued unless the patient is experiencing methadone-induced intoxication, sedation, or arrhythmias. If it is rapidly tapered, the dose should be carefully readjusted as withdrawal symptoms emerge.

15.3.6 Initiating MMT in Hospital

The treating physician may initiate MMT in hospital for pregnant patients, and for seriously ill patients who require prolonged hospitalization and who might leave against medical advice if their withdrawal is not promptly treated (Aszalos et al. 1999). Vigilance is required, as overdose deaths have occurred even in an inpatient setting. (See Section 12.0 Methadone Toxicity)

15.3.7 Opioid Detoxification with Methadone

Inpatient methadone detoxification should only be done by experienced MMT providers in a setting which provides 24 hour nursing and medical coverage. As the patient is closely monitored before and after dosing small p.r.n. doses can be used (e.g., 5 mg q.8.H. no more than 10-15 mg per day). The fixed morning dose can be increased by 10 mg every 2-3 days if the patient requires regular p.r.n. doses. The severity of their withdrawal can be measured using the Clinical Opiate Withdrawal Scale (COWS). Concurrent use of benzodiazepines or other sedating drugs should be avoided.

15.3.8 Discharge from Hospital

If the dose has been adjusted during hospitalization, the hospital MMT physician should advise the community MMT physician and the patient should be advised to return the pre-hospitalization take-home doses to the pharmacy.

16. Telemedicine in the Delivery of MMT

16.1 Overview

"Telemedicine" (TM) is the delivery of health-related services and information using telecommunications technologies such as two-way videoconferencing systems and tele-diagnostic instruments such as digital stethoscopes, otoscopes and patient examination cameras. The main provider of telemedicine infrastructure in Ontario is the Ontario Telemedicine Network (OTN), an independent, not-for-profit organization funded by the Government of Ontario.

In general TM allows the physician using the services of the OTN to interact with patients through a video monitor in a remote location.

TM appears to work best for patients who have achieved stability with their treatment plan and who have already developed a good working relationship with their MMT physician.

There is recognition that remote communities face special challenges accessing MMT and those specific strategies need to be considered to ensure the success of MMT in these communities.

It is the position of the Methadone Committee of the College that while TM can support treatment in communities where none exists, it is not a replacement for face-to-face interaction.

According to the CPSO, the use of TM by MMT physicians to provide MMT to patients in areas generally not able to access MMT is growing.

►Standards

For the best care to patients receiving MMT via TM, MMT physicians shall ensure the following:

S16.1	The site where the service is provided must be an accredited OTN site which means the videoconferencing equipment has been implemented according to OTN's network architecture, security and training standards to ensure conformance with the high technical and quality videoconferencing standards necessary for clinical care and PHIPA.
S16.2	At the MMT TM, site there must be a nurse with training specific to MMT to work with the patient to ensure their UDS is collected for the purpose of MMT physician interpretation.
S16.3	Supportive counselling and case management must be available to the MMT patient in-person onsite.
S16.4	Each location using delegation to administer methadone adheres to the CPSO policy entitled: *Methadone Maintenance Treatment for Opioid Dependence* (available at www.cpso.on.ca.)
S16.5	All patients must be assigned a most responsible MMT physician.
S16.6	The initial visit is conducted in-person with the results of a focused physical assessment available prior to initiation of MMT. In extenuating circumstances where the MMT physician is not able to see the patient in person and delaying treatment may result in harm to the patient, the MMT physician may do the initiation via TM but must see the patient in person within a reasonable time period (i.e., 4 -6 weeks).

When initiating MMT in remote communities, MMT physicians must consider sustainability, which includes planning and collaboration regarding local supports, secondary impacts on local health and social services, and transportation of methadone into the communities.

►Guidelines

G16.1	When initiating MMT in remote communities, the MMT physician should ensure the following: 1) Support of a local clinic team that is skilled and knowledgeable about MMT, is available to the patient 2) Face-to-face interaction 3) Partnerships with interdisciplinary services in the community to support patients on MMT are established 4) Arrangements with local hospitals and other healthcare providers are in place for patients to handle emergencies such as overdose 5) Appropriate methadone is available in advance of offering the service – ideally in the form of a local pharmacy and pharmacists who are part of the healthcare team in the community 6) Where methadone is shipped in for dispensing at the clinic, back up arrangements are in place with a local pharmacy in case of emergency such as delivery problems during bad weather.

Appendix A: Diagnostic Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
    a) the need for markedly increased amounts of the substance to achieve intoxication or the desired effect;
    b) markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
    a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances);
    b) the same (or a closely related) substance is taken to relieve (or avoid) withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple physicians or driving long distances), use the substance (e.g., chain smoking), or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was worsened by alcohol consumption).

Specify if:

With Physiological Dependence: evidence of tolerance or withdrawal (e.g., either Item 1 or 2 is present).

Without Physiological Dependence: no evidence of tolerance or withdrawal (e.g., neither Item 1 nor 2 is present).

Appendix B: Drug to Drug Interactions

Physicians need to be aware of common methadone-drug interactions. Many of these interactions involve the cytochrome P450 (CYP450) enzymes. While there are more than 28 CYP enzymes (Flexner and Piscitelli 2000; Shannon 1997; Wilkinson 2005, as cited in Levitt, 2005) the most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. As Levitt (2005) points out, some P450 interactions may be potential (i.e. theoretical), others are currently being investigated to confirm their clinical significance.

Of importance to physicians is how the substances that interact with the CYP450 system work to increase or decrease the level of methadone. Substances may act as substrates, inhibitors or inducers, as outlined in the table below:

Substrates, Inhibitors and Inducers

Substrate	Any drug metabolized by one or more CYP enzymes
Inhibitor	Any drug that slows the metabolism of drugs that are substrates, which may result in excessively high drug levels
Inducer	Boosts the activity of specific CYP enzymes resulting in more rapid metabolism of substrate drugs, which may result in lower than expected levels of substrate drugs.

Pharmacodynamic

Additive effects of:

- Another central nervous system (CNS) depressents, e.g., alcohol, benzodiazepines, other sedating medications e.g. dimenhydrinate, clonidine, when combined with methadone
  - High risk patients for toxicity on initiation
  - Risk of CNS depression during treatment.

- Medications causing similar effects e.g., constipation or urinary retention by anticholinergics.

- Medications causing prolongation of QTc interval e.g., tricyclic antidepressants, cocaine (see http://www/azcert.org/medical-pros/drug-lists/printable-drug-list.cfm and other websites).

Pharmacokinetic

Methadone is metabolized by several CYPs, predominantly by 3A4 enzyme system and to a lesser extent CYP 2B6, 2D6 and 1A2. Others may also be involved.

Important Considerations in Methadone Interactions

Some important considerations in methadone interactions are noted in the table below:

With Medications that are 3A4 Inhibitors	With Medications that are 3A4 Inducers
Fast onset	Slower onset
Possible increase in methadone effects including toxicity and overdose	Can result in decreased methadone effects and withdrawal symptoms
Extra care required during initiation of methadone	

Clinicians should take special care when medications are started or discontinued.

The following websites may be consulted:

http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf)
www.hivclinic.ca/man/drugs_interact.html

Appendix C: Initial Patient Assessment Form

ABOUT YOURSELF:

Please complete the following questionnaire as accurately and honestly as possible so that we can determine what kind of treatment would serve you best.

NAME _____ _____
(first) (last)
DATE _____
HEALTH CARD # _____ VERSION CODE: _____
DATE OF BIRTH _____
(year/month/day)
ADDRESS _____ APT # _____
CITY _____ POSTAL CODE _____
PHONE day ( ) _____ evening ( ) _____

CONTACT IN CASE OF EMERGENCY (state relationship)
_____

CONTACT'S PHONE ( ) _____

WHO REFERRED YOU? _____

GENDER: ❑ male ❑ female

DRUG HISTORY:

DRUG	AMOUNT USED	HOW LONG DAILY USER	ROUTE TAKEN	FIRST USED	LAST USED
Heroin					
Other Narcotics					
Cocaine					
Barbiturates (Fiorinal)					
Amphetamines					
Alcohol					
Cannabis (Pot, Hash)					
Cigarettes (packs per day)					
Benzodiazepines (Valium, Ativan)					

PRESCRIPTION MEDICATIONS:

(Any medications you regularly take or are prescribed, amount and frequency): none ❑
or, give details_____
_____
_____

Are you now or have you ever been prescribed narcotics (e.g., Tylenol #3, Percodan, Percocet, Dilaudid, Talwin, morphine) for an extended period of time (e.g., for more than four weeks?) ❑ yes ❑ no narcotic name _____

Amount prescribed _____ (per week/month) For how long?_____ (weeks/months/years)

For what reason was it prescribed?
_____
_____

If it has been discontinued, when and why? _____
_____

DRUG ALLERGIES:

none ❑ or, give details:
_____
_____

(any medications you can't take, and WHY NOT?)_____
_____

PAST MEDICAL HISTORY: (circle and give year)

Hepatitis A..... …neg/pos/never tested/don't know
Hepatitis B.....neg/pos/immune/vaccinated/carrier/never tested/don't know
Hepatitis C.....neg/pos/never tested/don't know
HIV..... ……...neg/pos (_____)/never tested/don't know
date of last test
Tuberculosis skin test..... neg/pos (_____)/never tested/don't know
date of last test
For the above questions, where was the test done, and where are the results now?
_____
_____

Year of first i.v. drug use . . (_____)/never
History of needle sharing. . yes/no
(including cotton, spoons, filters, etc.)
overdoses . . . . . yes/no
asthma . . . . . yes/no
seizures . . . . . yes/no
operations . . . . . yes/no
migraines . . . . . yes/no
back problems . . . . . .yes/no
ulcers . . . . . yes/no
heart problems . . . . . .yes/no
car accidents . . . . . yes/no
other: _____
(give year and type): _____

Name and address of your family doctor: _____

Is your doctor aware of your drug problem? ❑ yes ❑ no

WOMEN ONLY:

1. When was the first day of your last menstrual period ?_____
2. Current method of contraception ? The Pill/condoms/other:_____
3. Is there any chance you might be pregnant ? ❑ yes ❑ no

EMOTIONAL HEALTH:

Have you ever been treated by a family doctor or psychiatrist for:

anxiety? ❑ yes ❑ no

depression? ❑ yes ❑ no

Have been admitted to a psychiatric facility? ❑ yes ❑ no

Received treatment for any other emotional problems? ❑ yes ❑ no

Were you abused? (mentally, sexually or physically?) ❑ yes ❑ no

Have you ever attempted suicide? ❑ yes ❑ no

Are you currently depressed or suicidal? ❑ yes ❑ no

FAMILY HISTORY:

(Any family history of medical problems like alcohol or drug abuse, depression, heart disease etc.)

mother: _____ father:_____
(age) (age)
brothers, sisters, others _____

DRUG TREATMENT PROGRAMS:

(Including attempts at detox), program name, when, how long did you stay clean/ why failed?
1. _____
2. _____
3. _____

SOCIAL HISTORY:

Are you: married/single/separated/divorced/common-law/widowed
Children?_____ Whose custody are the children in? _____

Who lives in your household? _____

Do they abuse alcohol/drugs? ❑ yes ❑ no

Are the people close to you aware of your drug problem? ❑ yes ❑ no

Usual occupation: _____ Are you currently employed ? ❑ yes ❑ no

Last job held: _____ From when _____ to _____

Highest level of education: _____

Are you receiving: welfare/FBA/pension/UI/none/other?

Do you drive a car? ❑ yes ❑ no

LEGAL STATUS:

1. Are you currently on probation or parole? ❑ yes ❑ no
if yes, until when ? _____

2. Is treatment a condition of your probation? ❑ yes ❑ no
if yes, when ? _____

3. Do you have any Court dates pending? ❑ yes ❑ no
if yes, when ? _____

4. Do you have previous convictions? ❑ yes ❑ no
if yes, for what ?_____

5. Have you been incarcerated? ❑ yes ❑ no
if yes, for what ?_____

6. How long have you been in jail for in total? _____

7. Have you been charged with impaired driving? ❑ yes ❑ no

8. Have you been charged with a crime that included a weapon or violence? ❑ yes ❑ no

ABOUT YOUR ADDICTION:

In the last 12 months:
Do you need more and more of the drug you are using to get the same effect? ❑ yes ❑ no
Describe what symptoms you experience if you suddenly stop taking the drug:
_____
_____

Do you frequently take more drugs than you planned, or use it for longer than you planned to? ❑ yes ❑ no

Have you had many unsuccessful attempts to cut down on your drug use? ❑ yes ❑ no

Do you spend a lot of your day getting, using, and recovering from the effects of drugs? ❑ yes ❑ no

Have you given up work, social or other things you used to do because of your drug use? ❑ yes ❑ no

Do you keep taking drugs, despite the harm and problems it is causing you? ❑ yes ❑ no

Why have you come for treatment at this time? _____
_____

What type of treatment do you feel that you need?_____
_____

What are your goals for treatment? _____
_____

PHYSICAL EXAM:

Name: _____ Date of exam: _____

GENERAL _____ BP_____ /_____
HR _____ /min
PUPILS: normal/pinned/dilated FUNDI
CHEST: clear/other
CVS: murmur/other
ABDO: tender enlarged liver/spleen other
SKIN: tracks abscess tattoos piercing other
LYMPHADENOPATHY: ❑ yes ❑ no
OTHER: _____

ASSESSMENT:
Meets criteria for opioid dependence: _____
Suitable for medical detoxification:_____
Suitable for methadone: _____
Co-morbidity: _____
Psychiatric: _____
Medical: _____

Concurrent substance abuse: Benzo/Cocaine/Crack/Etoh/Barbs/Amp/THC

PLAN:
1. MEDICAL DETOX – discussed risks/ handout given/ patient declined detox
2. BLOOD WORK – including pretest counselling for HIV, Hepatitis B, C
3. METHADONE BENEFITS/DRAWBACKS – discussed
4. LETTER OF UNDERSTANDING COPY GIVEN REVIEWED SIGNED
5. UDS DRUG SCREENS FOR TOXICOLOGY
6. RELEASE OF INFORMATION SIGNED
7. REFERRED FOR SECOND ASSESSMENT (if needed)
8. RETURN FOR CPE ON: _____
9. OTHER:_____

Physician's signature: _____ Date: _____

Appendix D: Sample Methadone Maintenance Treatment Agreement

The prescribing and dispensing of methadone is regulated by provincial guidelines, as well as policies unique to Dr. _____'s practice. This contract has been prepared to both inform you about methadone maintenance therapy, as well as to document that you agree to the rules/ obligations contained in this agreement.

MMT Program Rules

It is important that the patient receive clear information about the MMT program rules and expectations. Policies on take-home doses, urine drug screens, appointments, and treatment withdrawl should be specified. The MMT physician should provide a copy of the treatment agreement to the patient and revisit it once the patient is stabilized.

Acknowledgments:

I acknowledge that:

1. Methadone is an opioid (opioids are drugs like heroin, codeine, morphine, Percocet, etc.), and that I will develop a physical dependence to this medication. Sudden decreases in dose or discontinuation of this medication will likely lead to symptoms of opioid withdrawal.

2. I am already physically dependent on at least one form of opioid and I'm unable to discontinue the use of opioids.

3. I have tried to the best of my ability other possible treatments for opioid dependence, and these attempts have been unsuccessful.

4. Taking any mood altering substance with methadone can be potentially dangerous. There have been reported deaths caused by the combination of methadone with alcohol, opioids, cocaine, barbiturates, and/or tranquillizers.

5. I may voluntarily withdraw from the methadone treatment program at any time.

6. It is important to inform my physician/dentist who is prescribing an opioid that I am taking methadone. I understand that a failure to do so is considered double doctoring, which is a criminal offence.

7. Regarding pregnancy, I understand that there can be effects on the developing fetus caused by methadone, and that specialized care will be required to reduce any harm to my fetus if I am or become pregnant while on methadone.

8. It is unsafe to drive a motor vehicle or operate machinery during the stabilization period after starting methadone and during dose adjustments.

9. Poppy seeds and certain over-the-counter medication may result in a positive drug UDS drug screen screen.

10. The common side effects of methadone are sweating, constipation, decreased sexual function, drowsiness, increased weight, and water retention. These are usually mild and can be lessened with assistance from my doctor. There are no known serious long-term effects from taking methadone.

11. I acknowledge that Dr. _____ is not my family doctor.

12. Methadone treatment will be discontinued or tapered if my physician determines that it has become medically unsuitable (i.e., the treatment is not effective or I develop a medical condition that could be made worse by methadone administration).

Behaviour while in our clinic

I understand the following behaviour is not acceptable in the clinic and may result in the termination of treatment:

1. Any violence or threatened violence directed toward the staff or other patients.

2. Disruptive behaviour in the clinic or the surrounding vicinity of the methadone clinic.

3. Any illegal activity, which includes selling or distribution of any kind of illicit drug in the clinic or the surrounding vicinity of the methadone clinic.

4. Any behaviour that disturbs the peace of the clinic or the surrounding vicinity of the methadone clinic.

I agree to maintain positive, respectful behaviour towards other program patients and staff at all times when in the clinic. Threats, racist or sexist remarks, physical violence, theft, property vandalism or mischief, the possession of weapons, and selling or buying illicit substances while on clinic property are extremely serious program violations and may result in the termination of my treatment.

Obligations of being on this program

1. I agree to take only one dose of methadone a day, and to have the ingestion of my dose witnessed on those days that I don't have carries (take-home methadone).

2. It is important to inform any prescribing physician or dentist who may treat me for any medical or psychiatric condition that I am receiving methadone, so my treatment can be tailored to prevent potentially dangerous interactions with methadone. I will bring any prescriptions and/or medication bottles that I receive from other doctors to appointments with Dr._____.

3. I agree to provide a supervised UDS drug screen sample for a drug screen when I receive a prescription for methadone.

4. Failure to provide a UDS drug screen sample may mean that my record will be marked as a sample assumed to contain drugs and that this could reduce my level of carries.

5. I understand that tampering with my UDS drug screen sample in any way is a serious violation of the program, and it may affect my future status in the program.

6. I understand that counselling is highly recommended while I am in the program.

7. I agree to keep all my appointments with the physician who is prescribing methadone for me. Repeatedly missing appointments may result in the reduction of my carry status and could interfere with the doctor-patient relationship. The physician is not obligated to fax a methadone prescription without an assessment.

I understand that I will not be given a dose of methadone if I:

1. Appear to be intoxicated or under the influence of some other substance. I may be asked to see a physician. For the sake of my own physical safety, I may be asked to wait before receiving my dose, or refused a dose for that day.

2. Arrive late, after the clinic/pharmacy hours.

3. Exhibit threatening or disruptive behaviour towards any staff member or another patient.

4. Do not show proper identification before receiving methadone, if asked for identification.

5. Miss more than three doses of methadone in a row.

Consents

1. I allow my physician to report to the CPSO of Physicians and Surgeons of Ontario (CPSO) my name, date of birth, OHIP number, city of residence, and the date methadone was initiated. The CPSO will keep this information confidential. This is done to prevent double doctoring.

2. I allow the CPSO or its designate permission to review my medical chart. This is done to assess the care provided by my physician and is not meant to judge my recovery.

3. I allow my methadone prescribing physician to speak to other doctors or health care professionals about my care.

4. I allow the clinic's pharmacist and nursing staff to speak to pharmacists or other health care providers to verify my recent methadone dose(s), which I received in another pharmacy or facility.

Confidentiality

Everything that you tell the clinic staff is confidential, although it is important to realize that under exceptional circumstances we can be obliged to report something you tell us to the appropriate authority. This can occur under the following conditions:

1. If we suspect that a child is at risk of emotional or physical harm or neglect, under the Child and Family Services Act, it is the law that we report this information.
2. If you become suicidal, homicidal, or are unable to take care of yourself due to a psychiatric condition, you might be held to be assessed by a psychiatrist against your will.
3. If you reveal to the staff that you intend to harm another person, we will be obliged to protect that person by notifying the appropriate authority.
4. If a Court subpoenas your medical chart, we must release it in accordance with the subpoena.
5. If it is suspected that you are unable to drive an automobile due to a medical condition (which includes intoxification from alcohol or drugs), we are obliged to notify the Ministry of Transportation of this.
6. Certain infections must be reported to the local public health department, e.g., tuberculosis, HIV.

I agree to respect the confidentiality of other patients in the program. My signature below indicates that I agree to follow the obligations and responsibilities outlined in this agreement. Should I fail to meet the terms of this agreement, I understand that I may be asked to leave the methadone program. *I have had an opportunity to discuss and review this agreement with my attending physician and my questions (if any) have been answered to my satisfaction.*

_____ _____ _____

Dated (dd/mm/yyyy) Patient's Name Patient's Signature

_____ _____ _____

Dated (dd/mm/yyyy) Physician's Name Physician's Signature

Appendix E Patient Initiation to MMT Form

Instructions to complete the Patient Initiation to MMT Form are as follows:

Section A:

This section must be completed in full for all patients

Any forms that do not have all information filled out will NOT be processed

Section B:

The physician starting treatment must identify their last name and treatment site

Please check the appropriate practice type box to ensure the patient is started at the correct treatment site in the database

This section must be signed and dated by the physician initiating treatment

Stamped signatures are acceptable however the physician is responsible for any records that may be false in this case

Section C:

This section can only be filled out if the patient is being transferred to another physician within the same treatment site.

A patient cannot be transferred to another clinic location using the transfer section – a cessation must be submitted in this case

A patient cannot be transferred to another clinic location with the same physician using the transfer section – a cessation must be submitted in this case.

Both physician signatures must be provided otherwise the form will not be processed

Section D:

This section must be signed by a physician within the same clinic

Please ensure the cessation date is not BEFORE the initiation date

Patient Initiation to MMT Form

A. PATIENT INFORMATION *(Print Clearly)*

THIS SECTION MUST BE COMPLETED FOR ALL PATIENTS

HAS THIS PATIENT BEEN ON A METHADONE PROGRAM BEFORE? *Yes* ☐ *No* ☐

Last Name:_____ GENDER: M☐ F☐

First/Middle Names: _____

DOB (mm/dd/yyyy): _____/_____/_____ CITY OF RESIDENCE: _____

DOES THE PATIENT HAVE INSURANCE? ☐ *Yes* ☐ *No*

Ontario Card #: _____ Other Provincial Card #: _____ Province: _____

I GIVE CONSENT TO THE FOLLOWING:
The CPSO of Physicians and Surgeons of Ontario will respect the confidentiality of my medical information
The CPSO of Physicians and Surgeons of Ontario will maintain the information in a database
The use of information on this form will be used for statistical purpose

PATIENT SIGNATURE:_____ DATE (MM/DD/YYYY):_____

B. INITIATION INFORMATION

DATE PATIENT IS STARTING TREATMENT WITH YOU (MM/DD/YYYY): _____/_____/_____

PRACTICE TYPE: ☐ INDEPENDENT PRACTICE ☐ *CORRECTIONAL* ☐ *COMMUNITY CLINIC*

NAME OF THE TREATMENT SITE: _____

TREATING PHYSICIAN'S NAME: _____

PHYSICIAN SIGNATURE _____ DATE (MM/DD/YYYY):_____/_____/_____

C. TRANSFER INFORMATION

CURRENT PROVIDER NAME/LOCATION : _____

DATE OF *TRANSFER* – CURRENT PROVIDER (MM/DD/YYYY): _____/_____/_____

CURRENT PHYSICIAN'S SIGNATURE: _____ DATE (MM/DD/YYYY): ____/____/___

NEW PROVIDER NAME/LOCATION: _____

NEW PHYSICIAN'S SIGNATURE: _____ DATE: (MM/DD/YYYY): ___/____/___

D. CESSATION INFORMATION

DATE OF LAST DOSE UNDER YOUR CARE (MM/DD/YYYY): ____/____/_____

PHYSICIAN'S SIGNATURE:_____ DATE (MM/DD/YYYY):____/____/___

Appendix F: Sample Prescription Form

Methadone Prescription Form

Name	Date	File #

Rx Methadone _____ mg _____
p.o. dispensed daily mixed in orange drink. Dose in words

Start Date: _____ End Date: _____ Inclusive

Drink observed in the pharmacy on days circled:

Mon Tue Wed Thur Fri Sat Sun

The following doses are to be dispensed as take-home doses:

Mon Tue Wed Thur Fri Sat Sun

Special Instructions:

Contact prescriber before filling this prescription if dose is increased by more than 15 mg, unless noted above. Hold prescription if more than three consecutive doses are missed, and contact prescriber. Notify the prescriber if a dose is missed. Fax a copy of this prescription to the prescriber if there are any concerns about this prescription.

_____ _____ M.D.
Signature Print Name

Prepared by	Date	Dispensed by

Appendix G Sample Physician/Pharmacist/Patient Agreement Letter

DR. XXXXXXXXXXX
XXXXXXXXXX Clinic
Address
Tel:# Fax#

Dear Pharmacist,

Our patient has requested to attend your pharmacy for Methadone Maintenance Treatment. We encourage an active communication between pharmacist and physician. The following safety measures, methadone dispensing practices, and clinic policies have been discussed with the patient. Please feel free to contact me to discuss any of these matters or any further suggestions that your team may have for this patient's clinical care. You may call/page me at _____. PLEASE DO NOT GIVE THIS PAGER/PHONE NUMBER TO THE PATIENT.

1. Patients are required to drink methadone dispensed in approximately 100 cc orange juice or orange juice substitute in front of the pharmacist. **The ingestion of methadone must be observed. Ask the patient to speak after their drink to ensure that it is being swallowed.**

2. The pharmacy team shall inform the methadone physician of any information or observed evidence of diversion of methadone.

3. The pharmacist shall inform the methadone physician of missed methadone doses by the patient. **In the first two weeks of treatment, if the patient misses 2 or more doses, the methadone dose must be withheld to prevent overdose.** The patient must be reassessed by the methadone physician before methadone is restarted.

4. **After the first two weeks of treatment, if three or more doses are missed in a row, the methadone dose must be withheld from the patient to prevent an overdose.** The patient must be re-assessed by the methadone physician before methadone is restarted. The pharmacy team shall inform the methadone provider of missed doses.

5. If there is any evidence of intoxication or sedation (slurred speech, stumbling gait, disorientation) **the methadone dose must be withheld** from the patient to prevent a possible overdose. The patient must be re-assessed by the methadone physician before methadone is restarted. The pharmacy team may contact the methadone physician to inform them of the observation of sedation.
   If the pharmacist observes evidence of an overdose, the patient will be advised that urgent medical care is required. The pharmacist may call 911 for transport to hospital. The pharmacist will contact the physician directly to inform them of the overdose and treatment directives.

6. Take-home doses should be dispensed in childproof bottles. Patients are advised to transport any take-home doses in a locked metal box to ensure community safety (i.e., to avoid

misplacement/loss and consumption of methadone by someone other than to whom it is prescribed). The pharmacist may request that the locked box be presented prior to issuing take-home doses.

7. Any doses of methadone vomited can only be replaced if the pharmacist or a member of the pharmacy team has witnessed the vomiting within 15 minutes of ingestion and informs the methadone provider of such.

8. The pharmacist or methadone physician may request that take-home dose bottles be returned to the pharmacy.

Thank you, _____

Appendix H: Sample Addiction Medicine Clinical Note

Name: _____
Date: _____

Current Methadone Dose: _____mg
Number of Take-home Doses: _____
Missed doses: Yes – No _____

Supervised UDS:
Methadone: _____
Cocaine: _____
Opiates: _____
Benzodiazepines: _____
Oxycodone: _____
Creatinine: Normal/Abnormal
Interpretation of UDS_____
Patient stated drug/alcohol use & route
Since last visit:
Opiates: Yes – No _____
Cocaine: Yes – No _____

Benzodiazepines: Yes – No _____
Alcohol: Yes – No _____

Other problematic drug use: Yes – No _____

Opioid Cravings: _____
None – Mild – Moderate – Severe

Opioid Withdrawal:
None – Mild – Moderate – Severe

Opiate Withdrawal Symptoms:
None – Insomnia – Anxiety – Dysphoria – Nausea - Diarrhea - Hot flashes – Irritably Myalgia - Restlessness – Rhinorrhea – Sneezing – Sweats - Yawning - Pupil dilated – Malaise – Abdominal Cramping – Piloerection

Timing of Withdrawal from Last Dose: _____

Counselling/Clinical Notes:

Psychological Issues Update:
Mood: Normal - Other
Sleep: Normal - Insomnia
Anxiety: Absent - Present
Energy: Normal – Other _____
Suicidal Ideation: Absent - Present - NA

O/E:
Appearance: Alert – Intoxicated
Behaviour: Normal – Abnormal
Gait: Normal – Abnormal
Speech: Normal – Abnormal
Eye contact: Normal – Abnormal

Reported methadone sedation: Yes – No

Reported methadone withdrawal: Yes – No

Take-home dose safety issues discussed: Yes – No – NA

Reviewed dangers of methadone diversion: Yes – No – NA

Clinically stable: Yes – No

Take-home doses locked up in a box: Yes – No – NA

Safe with take-home doses: Yes – No

Stable housing: Yes – No

Stable employment/ social support: Yes – No
Reported methadone withdrawal: Yes – No

Plan:
Rx: Methadone _____ mg po od from _____ to _____

Take-home doses: M T W T F S S for _____ week (s) RTC _____day/week

Appendix I: Managing Potential Methadone Overdose

This appendix includes documents to assist physicians in handling a potential methadone overdose. These materials are also intended to provide advice to patients and emergency room staff, and ensure that physicians who prescribe methadone have taken the necessary steps to avoid an adverse outcome in a methadone overdose scenario.

Reducing Risk of Toxicity During Initiation

Patient education

- The patient is to limit driving or use of machinery after a dose increase, particularly in the first few hours after dosing.
- The patient is to take the methadone dose in the morning, since the risk of overdose is increased at night.
- Whenever feasible (with the patient's consent), a family member or significant other should be educated about the symptoms of toxicity with instructions to go to the emergency department immediately at the first sign of toxicity. A patient information guide may be used for this purpose (See Appendix I (ii)).

Explain the risks of diverted methadone

- A single dose of methadone can be fatal.
- Patients are responsible for the safe storage of their methadone (See Appendix K).

Frequency of visits

- The MMT physician shall see the patient at least every one to two weeks.
- Twice-weekly visits during the first two weeks of treatment are recommended, particularly if the patient is at increased risk for methadone toxicity or cannot be stabilized at a low dose. If possible, the visits should be scheduled for two to six hours after the methadone dose. The MMT physician should inquire about sedation and other side effects.

Take-home doses

- No take-home doses shall be granted during the first month of treatment.
- It is recommended that no take-home doses be given for the first two months unless necessary (undue hardship, pharmacy closed on Sunday) and the reason for this should be documented in the patient's chart.

Avoid prescribing any sedating drugs

- Includes benzodiazepines, non-benzodiazepine hypnotics, antipsychotics, antidepressants, and sedating antihistamines. Even moderate, therapeutic doses of these drugs may increase the risk of toxicity if they are initiated at the

same time as methadone and the patient is not fully tolerant to their sedating effects.

- Patients should also be advised to avoid alcohol and over-the-counter sedating drugs.

Tapering High-dose benzodiazepine user

- Benzodiazepine abuse and dependence are common in this population.
- As with opioids, it is difficult to accurately judge a patient's benzodiazepine use and tolerance.
- Benzodiazepine tapering, while difficult on its own, can be very complicated and potentially unsafe when attempted with MMT initiation.

Intoxication or sedation

- At any stage of MMT, the pharmacist should be instructed to alert the MMT physician if the patient appears sedated or intoxicated.
- Intoxicated patients should not be medicated until assessed by their MMT physician.
- If signs of intoxication are observed after ingestion of methadone, the patient should be sent to the hospital by ambulance for assessment.

ii) Patient Information Sheet on Methadone Overdose

Methadone overdose (receiving a larger dose of methadone than intended) is a serious medical emergency.

Methadone is a long-acting medication and can stay in your body for many hours.

Even if you have been on methadone for a long time, taking more methadone than your body is used to can be dangerous. Even what may seem like a small dose increase can be dangerous.

If you are new to methadone or have not been taking your regular dose, even for a few days, **you are at increased risk of overdose**.

Taking too much methadone can result in difficulty breathing (slow or shallow breathing), drowsiness, small pupils, and, in some cases, coma and death.

For this reason, your nurse, pharmacist or MMT physician has deemed that **IT IS ESSENTIAL THAT YOU GO TO THE EMERGENCY DEPARTMENT** to be observed for a minimum of 10 hours, and maybe longer, depending on your symptoms.

There is good treatment available in the emergency department that can reverse the effects that you may get from taking too much methadone.

iii) Avoiding Overdose in the First Two Weeks of Methadone Treatment: A Guide for Patients and Their Families

Methadone is a very safe drug, but accidental overdoses sometimes happen, particularly in the first two weeks of treatment. The questions and answers below will help you get through this period safely. Share this information sheet with a friend or family member.

Why can't my doctor increase my dose more quickly?

When you first start methadone, you want to get on the right dose as soon as possible. But your doctor has to increase your dose slowly over several weeks, because your body takes time to adjust to methadone, and (unlike other narcotics), methadone builds up slowly in your bloodstream over several days. A dose that may feel like too little on a Monday could put you in hospital by Thursday.

What can I take to relieve withdrawal and help me sleep until the methadone begins to work?

Substances that make you relaxed or sleepy can be dangerous. This includes alcohol, opioids, benzodiazepines (Ativan, Valium, Rivotril, etc.), antihistamines such as Gravol or Benadryl, and certain types of antidepressants and tranquilizers.

Even certain antibiotics can be dangerous, by blocking the breakdown of methadone in the body. So make sure to check all your medications with your methadone physician

Isn't methadone supposed to make you sleepy?

No. You are supposed to feel normal on methadone, not high or sleepy. Methadone builds up so slowly that someone can feel sleepy during the day, lie down for a nap and not wake up.

How do I know if my methadone dose is too high?

• You may feel sleepy, and nod off several times during the day;
• You may be forgetful;
• You may be difficult to wake up from your sleep;
• You may experience slurred speech, stumbling walk, or appear drunk.

If these things occur you must call your doctor immediately or go to Emergency.

What precautions can I take to prevent overdose?

• Only take your methadone in the morning.
• See your doctor twice a week for the first two weeks.
• Don't take benzodiazepines, alcohol or other sedating drugs
• Discuss your methadone treatment with a close friend or family member. If they see that you're drowsy, they must call your methadone doctor or an ambulance.

I've been offered a small amount of methadone by a methadone patient at the pharmacy. This can't hurt — I know I need 80 mg and I'm only at 45 mg.

Above all, don't take any extra methadone. It's probably safe for your friend, but could be lethal for you. You took 80 mg **once** and were okay. If you had taken 80 mg every day for three or four days, you might have died. Remember, it takes five days for a certain dose to build up in your blood.

I'm receiving take-home doses. Is it safe to give a small amount of methadone occasionally to a friend who's not on methadone treatment, when he goes into withdrawal?

No it isn't safe, because your friend is not tolerant to methadone. A dose that is just right for you could be fatal for your friend.

iv) Emergency Department Management of Methadone Overdose

* NOTE: The methadone prescriber may send this form to the ED to assist them in managing a patient with a suspected methadone overdose.

Patient: _____

Physician:_____

Poison Centre Phone #: _____Physician Phone #:_____

Relevant details (to be completed by methadone provider):

- Usual methadone dose
- Dose of the suspected overdose (if known):
- Concurrent alcohol, benzodiazepine or other drug use
- Medications
- Relevant medical/psychiatric history
- Circumstances of the overdose (intentional or accidental):

Clinical Features of methadone overdose:

Methadone acts for at least 24 hours, much longer than other opioids. Symptoms begin up to 10 hours after the overdose. Early symptoms include nodding off, drowsiness, slurred speech and emotional lability. Respiratory depression occurs later.

ED protocol for managing suspected methadone overdose

Monitoring:

- Check frequently for vital signs, respiratory rate and O2 sat
- Hold a brief conversation to assess alertness.
- ECG and cardiac monitoring to check for prolonged QT interval and ventricular arrhythmias (methadone can cause toursades de pointes).

Medical Management with intubation or naloxone

Naloxone is a safe treatment in patients who are not physically dependent on opioids (e.g., patients not in methadone therapy who took methadone at a party). For methadone- or opioid-dependent patients, intubation avoids risks of naloxone-induced withdrawal. Intubation is necessary if:

- RR < 12; hypercapnia; persistent desaturation despite supplemental oxygen
- Patient fails to respond to naloxone within 2 min

Naloxone precautions:

- Ventricular dysrhythmias and cardiac arrest can occur with naloxone-induced withdrawal, especially if patients are withdrawing from other substances.
- Patients in naloxone-induced withdrawal may become agitated and leave against medical advice.
- Naloxone can induce emesis.

Above risks are avoided with intubation.

Naloxone dosing

- If the patient has severe respiratory depression, give 2.0 mg naloxone IV.
- If there is minimal respiratory depression, give 0.01 mg/kg weight to avoid precipitating withdrawal.
- If there is no response after the initial dose, repeat naloxone 2–4 mg every 2–3 min.
- If there is no response after 10–20 mg naloxone, search for other causes for the coma.
- If the patient responds to naloxone, infuse at 2/3 of the effective dose per hour.
- Give a bolus of 1/2 the effective dose 15–20 min after starting infusion.
- Titrate dose to avoid withdrawal, while maintaining adequate non-assisted respirations.

Recommended ED observation periods

- Observe for at least 10 hours post-overdose.
- Discharge if patient is completely asymptomatic during that time.
- If patient becomes symptomatic at any time during the 10 hours, monitor for at least 24 hours post-overdose.
- If patient is intubated or on naloxone, continue intubation/naloxone for at least 24 hours post-overdose.
- Monitor for at least **6 hours** after naloxone or intubation is discontinued.

Departure AMA: If the physician feels the patient is not safe to leave, a Form I should be completed and the patient should be forced to stay.

Discharge instructions: Tell patient not to take any methadone, alcohol or sedating drugs until seen by methadone physician the next day. Have a family member or support person observe overnight, and call an ambulance if the patient appears more drowsy, is difficult to arouse or snores much more loudly than usual.

v) Against Medical Advice (AMA)

Date:_____

I,_____ , acknowledge that _____ explained my condition to me and advised me of the potential risks and/or complications which could or would arise from refusal of medical care. I have also been advised that other unknown risks and/or complications are possible. Being aware that there are known and unknown potential risks and/or complications, it is still my desire to refuse the advised medical care.

I do hereby release _____ and _____ _____ *(clinic name)* from all liability resulting from any adverse medical condition(s) caused by my refusal of the recommended medical care.

Signature of Patient/Parent/Legal Guardian:
_____

Date_____

Witness _____

If witness acted as translator, check here _____

Name of translator_____

Appendix J: Opioid Withdrawal and Tolerance

Physicians titrating methadone must be familiar with the clinical features of opioid withdrawal.

Opioid Withdrawal

Opioid withdrawal peaks at 2–3 days after the last use. Physical symptoms largely resolve by 5–10 days, although psychological symptoms can continue for weeks or months.

Serious complications of withdrawal include miscarriage, premature labour, suicide, and overdose or relapse due to loss of tolerance.

Opioid Withdrawal Signs and Symptoms

Physical Symptoms	Psychological Symptoms	Physical Signs
Myalgia Abdominal cramps Nausea Chills Hot flashes Electric or uncomfortable feeling Yawning	Restlessness Dysphoria Insomnia Anxiety Irritability Fatigue Drug craving (the insomnia and anxiety may be severe and distressing)	Lacrimation Rhinorrhea Dilated pupils Abdominal tenderness Vomiting Diarrhea Sweating Chills Piloerection Tachycardia Hypertension

The patient on inadequate doses of methadone will describe a characteristic set of symptoms. The symptoms appear a certain number of hours after the methadone dose, although there may be some variation with the patient's activity level and other factors. The onset of symptoms is delayed with each dose increase.

Alternative explanations should be sought if the patient:

- gives an inconsistent history of withdrawal symptoms;
- has one isolated symptom (such as insomnia or nausea);
- advises the onset of symptoms is not related to the time of the dose; or
- has been taking a stable dose and suddenly complains of withdrawal (see below).

A dose might be considered acceptable if the patient sleeps comfortably at night and only has mild withdrawal symptoms on awakening, which are tolerable to the patient.

Conditions Commonly Confused with Withdrawal

The clinician should determine why the patient continues to report withdrawal symptoms despite dosage adjustment. Common reasons for ongoing withdrawal include:

- medication use that speeds methadone metabolism (such as phenytoin, chronic alcohol use)
- opioid use
- diverting doses

Physicians should consider a medication review with the pharmacist. The following conditions cause symptoms that are confused with withdrawal.

Pseudonormalization should be suspected if the patient regularly complains some weeks after a dose increase that it is no longer 'working.' Patients who are mildly intoxicated on opioids feel more enthusiastic and energetic. As they develop tolerance, they may feel they need a dose increase to recreate this effect, which they view as both desirable and normal.

Insomnia is often the dominant symptom of opioid withdrawal. Other causes should be ruled out if the patient reports insomnia that isn't accompanied by other withdrawal symptoms and is not relieved by a dose increase. Depression, anxiety, and use of alcohol and cocaine are common causes of insomnia in this population. A careful sleep history will identify day-night reversal, daytime napping and other causes of nighttime insomnia. Careful instruction in sleep hygiene should be undertaken. Medication should be used only when the patient is on a stable dose of methadone and sleep hygiene counselling has failed. Trazodone or other non-benzodiazepine hypnotics are the treatments of choice.

Sedation and Withdrawal Symptoms: Occasionally patients report sedation several hours after dosing, with withdrawal symptoms and insomnia at night. This can be difficult to sort out. The sedation may simply represent the onset of sleep following a night of insomnia due to withdrawal. The methadone dose might be too high, causing excessive sleep during the day and inadequate sleep at night. The patient may have day-night reversal, independent of the methadone dose.

Other conditions: Patients may be anticipating that an increase in their dose will manage symptoms that have little to do with withdrawal. Common examples include depression, anxiety, irritable bowel syndrome, and some forms of chronic pain. The physician should identify these symptoms, explain to the patient the limitations of MMT, and assist the patient in finding an appropriate management strategy.

Diagnostic Criteria for Opioid Withdrawal

A. Either of the following:

1) cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
2) administration of an opioid antagonist after a period of opioid use

B. Three (or more) of the following: developing within minutes to several days after Criterion A:

1) dysphoric mood
2) nausea or vomiting
3) muscle aches
4) lacrimation or rhinorrhea
5) papillary dilation, piloerection or sweating
6) diarrhea
7) yawning
8) fever
9) insomnia

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Medical Treatment of Acute Opioid Withdrawal

Buprenorphine

Buprenorphine tapering is substantially more effective than clonidine and other non-opioid treatments in reducing opioid withdrawal symptoms and retaining patients in treatment.

Protocol:

- Initial dose – similar to maintenance protocol (4-8 mg/day)
- Increase dose by 2-4 mg daily until therapeutic dose achieved (usual range 8-16 mg)
- Inpatients: Reduce dose by 2 mg every 1–3 days
- Outpatients: reduce dose by 2 mg every week
- Use adjuvant medications as necessary, eg antidiarrheals and anti-inflammatories (see below)

Clonidine

Outpatients:

- Clonidine 0.1 mg PO bid to tid
- May increase to 0.2 mg bid to tid after first day;
- Continue bid to tid for 3–5 days then PRN for 3–5 more days.

Inpatients:

- Check BP prior to each dose;
- Hold if BP < 90/60 or marked postural drop;
- May increase to 0.3 mg bid to tid.

Adjuvant medications:

- NSAID or acetaminophen for myalgia;
- Loperamide for diarrhea;
- Gravol or other antinauseant;
- Trazodone 50–100 mg HS for insomnia.

Precautions:

- Do not prescribe clonidine if BP < 90/60, patient pregnant, on antihypertensives or has heart disease.
- Warn patients about postural symptoms and drowsiness. Postural symptoms are dose-related, so be cautious with higher doses.
- Warn about mixing with opioids, or having prolonged hot bath (both can cause hypotension).
- Don't prescribe for longer than 2 weeks (rebound hypertension).
- Warn patients they're at risk for overdose if they relapse to their usual dose; always combine clonidine protocol with a documented treatment plan.

Tolerance

Tolerance is said to occur when higher doses are required over time to achieve the same effect, and the same dose has less effect over time. Tolerance to the psychoactive effects of opioids develops within days, and is lost within days.

Appendix K: Take-Home Dose Agreement

Methadone is a potent medication. A single dose taken be a person not used to taking Methadone or by someone using or abusing other medications or drugs can be fatal, especially if taken by a child. For this reason, I agree to the following:

1. I will store my take-home doses in a locked box, in a location where it is unlikely to be stolen or accidentally taken by another person. I will show this locked box to my physician is and when requested.
2. I will consume my dose(s) on the day(s) they are prescribed only. I will consume my Methadone dose in the appropriate manner (a full dose taken once every 24 hours orally).
3. I agree not to give, lend or sell my take-home doses to anyone. I understand that selling methadone is a criminal offence as well as a danger to the community.
4. Take-home doses are a privilege and not a right. These are granted by my physician in accordance with the clinic policies, the College of Physicians and Surgeons of Ontario MMT Program Standards and Clinical Guidelines and at the discretion of my prescribing physician.
5. Take-home doses are continued and increased once every 4 weeks so long as I continue to remain clinically stable and able to be responsible for the care of my take-home doses. This is again at the discretion of my prescribing physician.
6. Take-home doses may be cancelled or decreased if I do not remain clinically stable and able to be responsible for the care of my take-home doses.
7. Lost, spilled, vomited or stolen take-home doses may not necessarily be replaced. Lost or stolen take-home doses must be reported to the local police department.
8. I am aware that I can be called in for a random check of my take-home doses and on this occasion will bring my used and unused Methadone bottles to the pharmacy or clinic when asked to do so by my physician, pharmacist or clinic staff.
9. I will advise the clinic of any change in my contact information (phone number or address).

My signature below indicates that I agree to follow the obligations and responsibilities outlined in this agreement. Should I fail to meet the terms of this agreement, I understand that this will affect my ability to be able to partake in take-home dose program.
I have had an opportunity to discuss and review this agreement with my prescribing physician and my questions have been answered to my satisfaction.

_____	_____	_____
Patient's Name	Patient's Signature	Date
_____	_____	_____
Witness's Name	Witness's Signature	Date

Appendix L: Protocols for MMT and Pregnancy

Protocol for Inpatient Initiation (Finnegan 1991, Kaltenbach et al. 1998)

Methadone initiation should begin at the first sign of withdrawal. Based on our experience, the expected length of stay is approximately 5-7 days.

On day 1: Provide 10-20mg of methadone as an initial dose at onset of withdrawal symptoms, followed by supplemental 5mg every 4-6 hours if withdrawal symptoms are present.

On day 2: Provide previous day's total dose as a single morning dose, followed by supplemental 5mg doses every 4-6 hours for withdrawal symptoms

On subsequent days: continue as above until comfortable on one daily dose with no supplemental medications over a 24 hour period.

Most patients will be controlled on a daily dose of between 20-35mg of methadone after the first 2-3 days.

Subsequent dose increases will be needed as outpatients.

Protocol for Outpatient Initiation

If patient declines to be monitored on a daily basis for methadone dosing, follow the CPSO protocol for initiation of non-pregnant individuals. Frequent office visits every 3 days are recommended until the patient is stabilized on a maintenance dose.

1. Administer 10-20mg initial dose for first 3 days
2. Further dose increases of 5-15mg can occur every 3-5 days based on persistent withdrawal symptoms.

Alternatively, if patient can be re-assessed repeatedly during the day, the following outpatient protocol developed by Hoegerman and Schnoll (1991) can be considered.

1. Patient is advised to arrive at the clinic for first appointment of the morning.
2. On day 1: Assess for withdrawal. If withdrawal is mild to moderate, administer a starting dose of 15mg of methadone and observe for several hours for intoxication. Patient returns in the afternoon and is re-assessed for withdrawal. An additional 5-10mg of methadone may be provided.
3. On day 2: Administer previous day's total dose as a single dose in the morning and consider increasing dose by 10mg if still experiencing withdrawal. Additional doses for later on the day may still be needed.
4. On subsequent days: Administer methadone as above until patient can be converted to a single dose of methadone.
5. Do not exceed 35mg by day 3.

Maintaining a pregnant woman on methadone can continue as with any other patient. The patient should be seen every 1-2 weeks to re-assess her methadone dose.

Appendix M: Resources

1. Health Canada Office of Controlled Substances (613) 946-5139 or 1-866-358-0453 www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hecs-dgsesc/dscsp-psasc/index-eng.php

2. CPSO Methadone Program (416) 967-2661

3. The Drug and Alcohol Registry of Treatment (DART) 1-800-565-8603 or http://www.dart.on.ca.

4. ConnexOntario www.connexontario.ca

5. Ontario Poison Information Centre 1-800- 268-9017 or www.ontariopoisoncentre.com/poisoncentre

6. Ontario College of Pharmacists (416) 962-4861 or www.ocpinfo.com

7. Methadone Drug Interactions: www.atforum.com and/or www.drug-interactions.com

Glossary

Abuse, drug
Any use of an illegal drug, or the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness, e.g., "getting high." (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Addiction
A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Agonist
Drugs that interact with receptor sites to cause the same effect that natural chemicals would case at these sites. Karch, A, M. (2008). *Focus on nursing in pharmacology.* (4th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.

Agonist (Adopted 99.10.14)
A substance that acts at a neuronal receptor to produce effects similar to those of a reference psychoactive substance, e.g. methadone is an agonist at the opioid receptors.

Antagonist
Drugs that combine with receptors that do not begin a change in cell function. When antagonists bind to receptors, agonists are prevented from binding and causing an action. Gutierrez, K. (2008). *Pharmacotherapeutics: Clinical reasoning in primary care* (2nd ed.). Saunders: St. Louis.

Antagonist (Adopted Canadian Society of Addiction Medicine October 14, 1999)
A substance that counteracts the effects of a reference psychoactive substance by inhibiting or reversing its effects at a neuronal receptor site, e.g. naltrexone acts as an antagonist at the opioid receptor.

Concurrent Disorders (Adopted Canadian Society of Addiction Medicine October 14, 1999)
The presence of one or more primary, physical and/or psychiatric disorders that have an interactive effect on the course of Substance Dependence and require specific diagnosis and treatment in order to achieve stabilization and/or recovery.

Controlled Substance
There are many controlled substances listed under the *Controlled Substance Act.* These drugs are grouped under schedules. Below are examples of some of the better known drugs within each Schedule:

- Schedule I contains drugs made from the opium poppy such as heroin, codeine; drugs made from coca such as cocaine; and synthetically derived drugs such as methadone.
- Schedule II contains cannabis (marijuana) and its derivatives.
- Schedule III contains drugs such as amphetamines and lysergic acid diethylamide (LDS).

- Schedule IV contains drugs such as benzodiazepines and barbiturates.
- Schedule V and VI contain precursors required to produce controlled substances (National Association of Pharmacy Regulatory Authorities, 2002-2004).

Craving (Adopted Canadian Society of Addiction Medicine October 14, 1999)
A bio-psychological arousal and urge to return to addictive behaviour, characterized by a strong desire, pre-occupation and possible impulsivity.

Contingency Management
A type of treatment used in the mental health and substance abuse fields. Patients are rewarded (or less often, punished) for their behaviour; generally, adherence to or failure to adhere to program rules and regulations or their treatment plan.

Dependence, Physical
A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Diversion
The intentional transfer of a controlled substance from legitimate distribution and dispensing channels. (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Dose, stable
A "pharmacologically stable dose" is one that produces a fairly steady plasma level; it is established when the total daily dose is fixed for at least two weeks and:
1) frequency is scheduled and spread throughout the day, AND/OR
2) at least 70% of the prescribed opioid is controlled release.

Double-doctoring
Receiving a prescription for a narcotic, and then seeking and receiving another prescription or narcotic from a different practitioner without disclosing to that practitioner particulars of every prescription or narcotic obtained within the previous 30 days.(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Half-life
The time required for half of the total drug amount to be eliminated from the body. Generally after five half-lives, 97% of a drug will be eliminated.

Pharmacotherapeutics for Advanced Practice – A Practical Approach, Virginia Poole Arcangelo and Andrew M. Petersen, Second Edition, 2006.

Harm Reduction
A continuum of services that represent a philosophical, pragmatic approach to providing care while minimizing the negative outcomes associated with substance use. The focus is goal oriented,

humanistic and in keeping with a cost benefit awareness. (Pauly, Goldstone, McCall, Gold & Pyne, 2007). Pauly, B., Goldstone, I., McCall, J., Gold, F., & Payne, S. (2007). The ethical, legal and social context of harm reductions. *Canadian Nurse, 103,* 19–23.

Maintenance Therapy (Adopted 01.10.19)

Treatment of Substance Dependence by a prescription drug, to prevent withdrawal and reduce the harm associated with a particular method of administration, attendant dangers to health and/or social consequences, e.g. methadone for Opioid Dependence or nicotine replacement therapy (NRT) for tobacco.

Misuse, opioid

Use of an opioid in ways other than those intended by the prescribing physician (sometimes also called problematic opioid use).(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Narcotic

Any drug included in the "Schedule" under the Controlled Drugs and Substances Act: Narcotic Control Regulations. (Minister of Justice)

Opiate

A naturally-occurring or semi-synthetic compound derived from the opium poppy (papaver somnifer) (College of Physicians and Surgeons of Alberta, 2005).

Opioid

A compound having actions or properties similar to opiates. A broader term encompassing all opiates (such as heroin, morphine and codeine), as well as synthetic opiate-like compounds (such as methadone and fentenyl) (College of Physicians and Surgeons of Alberta, 2005).

A family of drugs that act by attaching to endogenous mu, kappa and delta receptors in the brain and share a common set of clinical effects, including analgesia, sedation, constipation, and respiratory depression. **Note**: Reference throughout this document to specific pharmaceutical products as examples does not imply endorsement of any of these products.

Pharmacodynamics

The set of processes by which drugs produce specific biochemical or physiological changes in the body-how the drug acts on the body

Pharmacotherapeutics for Advanced Practice – A Practical Approach, Virginia Poole Arcangelo and Andrew M. Petersen, Second Edition, 2006 (Archangelo & Peterson, 2006).

Pharmacokinetics

Examining the absorption, distribution, metabolism and excretion of a drug, the onset of action, the half life, peak effect and duration of effects – how the body acts on the drug.

Karch, A, M. (2008). *Focus on nursing in pharmacology.* (4th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.

Split doses
An alternative way of providing methadone to clients, consisting of two or more doses per day (so it is not ingested all at one time). It is used for clients who have demonstrated "rapid metabolism" of their once daily methadone dose (e.g. during third trimester of pregnancy) or are on medications that have been shown to induce rapid metabolism of methadone (i.e. certain HIV medications). A consultation with a experienced MMT provider should be considered in these circumstances. Split doses do not necessarily have to be equal; twice-daily observed ingestion may be necessary

(College of Physicians and Surgeons of Alberta, 2005).

Stable daily dose
Optimal daily dose of methadone that will relieve withdrawal symptoms, block opioid-induced euphoria and reduce drug cravings without sedation or other significant side effects

(College of Physicians and Surgeons Ontario, 2005).

Steady state
A constant mean concentration of a drug in the body, there are peaks and troughs in the drug level, but the fluctuations remain within a constant range

Pharmacotherapeutics for Advanced Practice – A Practical Approach, Virginia Poole Arcangelo and Andrew M. Petersen, Second Edition, 2006. (Archangelo & Peterson, 2006).

Substance
Any drug with pleasant psychoactive effects and addiction potential, including alcohol, illegal drugs, and prescription drugs.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Substance abuse (American Psychiatric Association, 1994)

- **A.** A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12 month period:
    1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).
    2. recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use).
    3. recurrent substance-related legal problems (e.g. arrests for substance-related disorderly conduct)
    4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights)
- **B.** The symptoms have never met the criteria of Substance Dependence for this class of substance.

Substance dependence
See addiction.

Substance dependence
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period (American Psychiatric Association, 1994)

A .Tolerance, as defined by either of the following:
i. a need for markedly increased amounts of the substance to achieve intoxication or desired effect; or
ii. markedly diminished effect with continued use of the same amount of the substance.

B.Withdrawal, as manifested by either of the following:
i. the characteristic withdrawal syndrome for the substance; or
ii. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

C. The substance is often taken in larger amounts or over a longer period than was intended.
D. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
E. A great deal of time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors or driving long distances), use the substance (e.g. chain-smoking), or recover from its effects.
F. Important social, occupational, or recreational activities are given up or reduced because of substance use.
G. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

With physiological dependence: evidence of tolerance or withdrawal (i.e. either Item 1 or 2 is present).
Without physiological dependence: no evidence of tolerance or withdrawal (i.e. neither Item 1 nor 2 is present).

Substance misuse
The use of a psychoactive substance (drug or alcohol) for a purpose other than that for which it was intended, and that cause's physical, social, and psychological harm. The term is also used to represent the pattern of use: experimental, recreational and dependent (Rassool, 2002).

Rassol, G. (2002) Substance misuse and mental health: An Overview. Nursing Standard, 16, 46-52.

Substance tolerance
A neurological adaptation to the psychoactive effects of a substance; more of the drug is required to achieve the same effect. Tolerance develops quickly to the psychoactive effects of alcohol and opioids. Highly tolerant clients can behave almost normally after consuming opioid doses that would be fatal in non-tolerant clients (Kahan & Wilson, 2002). Tolerance to the psychoactive effects of opioids develops within days, and is lost within days (CPSO, 2005).

A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Substance Use Disorders (Adopted Canadian Society of Addiction Medicine October 17, 2003)
A category of two disorders, namely, Substance Abuse and Substance Dependence, as in DSM IV.

Substance withdrawal
Characteristic syndrome produced by abrupt cessation of a drug.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Tapering
A gradual decrease in a dose of a drug; could result in a lower daily dose or cessation of the drug.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Titration
A technique of adjusting a dose until a stable/optimal dose is reached; usually means gradually increasing the dose to allow the body to develop tolerance and minimize adverse effects.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Tolerance
A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Withdrawal
Characteristic syndrome produced by abrupt cessation of a drug.

(Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain 2010)

Bibliography

Abramson DW, Quinn DK, Stern TA (2008) Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature. Prim Care Companion J Clin Psychiatry 10: 470-6

Albion C, Shkrum M, Cairns J (2010) Contributing factors to methadone-related deaths in ontario. Am J Forensic Med Pathol 31: 313-9

Amass L, Bickel WK, Crean JP, Higgins ST, Badger GJ (1996) Preferences for clinic privileges, retail items and social activities in an outpatient buprenorphine treatment program. J Subst Abuse Treat 13: 43-9

Amass L, Kamien JB, Mikulich SK (2001) Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. Drug Alcohol Depend 61: 173-81

Amato L, Davoli M, Minozzi S, Ali R, Ferri M (2005) Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev: CD003409

Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H (2009) Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction 104: 993-9

Archie C (1998) Methadone in the management of narcotic addiction in pregnancy. Curr Opin Obstet Gynecol 10: 435-40

Astals M, Domingo-Salvany A, Buenaventura CC, Tato J, Vazquez JM, Martin-Santos R, Torrens M (2008) Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment. Subst Use Misuse 43: 612-32

Aszalos R, McDuff DR, Weintraub E, Montoya I, Schwartz R (1999) Engaging hospitalized heroin-dependent patients into substance abuse treatment. J Subst Abuse Treat 17: 149-58

Australian Department of Health and Aging (2003) Principles of Drug Addiction Treatment: A Research-Based Guide, Canaberra, Australia

Backmund M, Schutz CG, Meyer K, Eichenlaub D, Soyka M (2003) Alcohol consumption in heroin users, methadone-substituted and codeine-substituted patients--frequency and correlates of use. Eur Addict Res 9: 45-50

Ball JC, Lange WR, Myers CP, Friedman SR (1988) Reducing the risk of AIDS through methadone maintenance treatment. J Health Soc Behav 29: 214-26

Banta-Green CJ, Maynard C, Koepsell TD, Wells EA, Donovan DM (2009) Retention in methadone maintenance drug treatment for prescription-type opioid primary users compared to heroin users. Addiction 104: 775-83

Bao YP, Liu ZM, Epstein DH, Du C, Shi J, Lu L (2009) A meta-analysis of retention in methadone maintenance by dose and dosing strategy. Am J Drug Alcohol Abuse 35: 28-33

Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. Journal of Opioid Management (2006) Sep;2(5):277-82.

Beauverie P, Furlan V, Edel YA (2001) Slow metabolism and long half life of methadone in a patient with lung cancer and cirrhosis. Ann Med Interne (Paris) 152 Suppl 7: 50-2

Bell GL, Lau K (1995) Perinatal and neonatal issues of substance abuse. Pediatr Clin North Am 42: 261-81

Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K (2003) Maternal methadone dose and neonatal withdrawal. Am J Obstet Gynecol 189: 312-7

Binder T, Vavrinkova B (2008) Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. Neuro Endocrinol Lett 29: 80-6

Bleich A, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M (1999) Correlates of benzodiazepine abuse in methadone maintenance treatment. A 1 year prospective study in an Israeli clinic. Addiction 94: 1533-40

Blinick G, Wallach RC, Jerez E (1969) Pregnancy in narcotics addicts treated by medical withdrawal. The methadone detoxification program. Am J Obstet Gynecol 105: 997-1003

Brands B, Blake J, Marsh DC, Sproule B, Jeyapalan R, Li S (2008) The impact of benzodiazepine use on methadone maintenance treatment outcomes. J Addict Dis 27: 37-48

Brands B, Blake J, Sproule B, Gourlay D, Busto U (2004) Prescription opioid abuse in patients presenting for methadone maintenance treatment. Drug Alcohol Depend 73: 199-207

Brands J, Brands B, Marsh D (2000) The expansion of methadone prescribing in Ontario, 1996-1998. Addiction Research 8: 485-496

Breslin KT, Malone S (2006) Maintaining the viability and safety of the methadone maintenance treatment program. J Psychoactive Drugs 38: 157-60

Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, Strasser F, Willey J, Bertolino M, Mathias C, Spruyt O, Fisch MJ (2004) Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol 22: 185-92

Burke BL, Arkowitz H, and Dunn C (2002) The eficacy of motivational interviewing and its adaptations: What we know so far. In W.R. Miller and S. Rollnick (Eds.), Motivational Intervewing: Preparing People for Change pp 217-250. New York: Guilford Press.

Byrne A (2009) Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med 151: 216; author reply 218-9

Cacciola JS, Alterman AI, Rutherford MJ, McKay JR, Mulvaney FD (2001) The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. Drug Alcohol Depend 61: 271-80

Callaly T, Trauer T, Munro L, Whelan G (2001) Prevalence of psychiatric disorder in a methadone maintenance population. Aust N Z J Psychiatry 35: 601-5

CAMH (2004) Centre for Addiction and Mental Health. Issac P, Kalvik A, Brands J, Janecek E (Eds). Methadone Maintenance: A Pharmacist's Guide to Treatment, 2nd edition.

CAMH (November 24, 2010) Centre for Addiction and Mental Health, Personal communication letter by CAMH pharmacists Eva Janecek, Annie Kalvik, Pearl Isaac, Beth Sproule.

Caplehorn JR, Bell J (1991) Methadone dosage and retention of patients in maintenance treatment. Med J Aust 154: 195-9

Caplehorn JR, Dalton MS, Cluff MC, Petrenas AM (1994) Retention in methadone maintenance and heroin addicts' risk of death. Addiction 89: 203-9

Caplehorn JR, Drummer OH (1999) Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. Med J Aust 170: 104-9

Caplehorn JR, Drummer OH (2002) Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. Aust N Z J Public Health 26: 358-62; discussion 362-3

Caplehorn JR, Ross MW (1995) Methadone maintenance and the likelihood of risky needle-sharing. Int J Addict 30: 685-98

Caputo F, Addolorato G, Domenicali M, Mosti A, Viaggi M, Trevisani F, Gasbarrini G, Bernardi M, Stefanini GF (2002) Short-term methadone administration reduces alcohol consumption in non-alcoholic heroin addicts. Alcohol Alcohol 37: 164-8

Carpenter KM, Brooks AC, Vosburg SK, Nunes EV (2004) The effect of sertraline and environmental context on treating depression and illicit substance use among methadone

maintained opiate dependent patients: a controlled clinical trial. Drug Alcohol Depend 74: 123-34

Chakrabarti A, Woody GE, Griffin ML, Subramaniam G, Weiss RD (2010) Predictors of buprenorphine-naloxone dosing in a 12-week treatment trial for opioid-dependent youth: secondary analyses from a NIDA Clinical Trials Network study. Drug Alcohol Depend 107: 253-6

Chang G, Carroll KM, Behr HM, Kosten TR (1992) Improving treatment outcome in pregnant opiate-dependent women. J Subst Abuse Treat 9: 327-30

Chasnoff IJ, Hatcher R, Burns WJ (1982) Polydrug- and methadone-addicted newborns: a continuum of impairment? Pediatrics 70: 210-3

Cheung O, Sterling RK, Salvatori J, Williams K, Hubbard S, Luketic VA, Stravitz TR, Sanyal AJ, Contos MJ, Mills S, Shiffman ML (2010) Mild Alcohol Consumption is Not Associated With Increased Fibrosis in Patients With Chronic Hepatitis C. J Clin Gastroenterol 45: 76-82

Chutuape MA, Silverman K, Stitzer M (1999a) Contingent reinforcement sustains post-detoxification abstinence from multiple drugs: a preliminary study with methadone patients. Drug Alcohol Depend 54: 69-81

Chutuape MA, Silverman K, Stitzer ML (1999b) Use of methadone take-home contingencies with persistent opiate and cocaine abusers. J Subst Abuse Treat 16: 23-30

Chutuape MA, Silverman K, Stitzer ML (2001) Effects of urine testing frequency on outcome in a methadone take-home contingency program. Drug Alcohol Depend 62: 69-76

Collège des médecins du Québec & Ordre des pharmaciens du Québec (2000) Clinical guidelines and procedures for the use of methadone in the maintenance treatment of opioid dependence, Quebec City

Corkery JM, Schifano F, Ghodse AH, Oyefeso A (2004) The effects of methadone and its role in fatalities. Hum Psychopharmacol 19: 565-76

Cornish R, Macleod J, Strang J, Vickerman P, Hickman M (2010) Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ 341: c5475

CPSO (2009) College of Physicians and Surgeons of Ontario Annual Report 2009, Toronto, ON

Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Towsend CO, Bruce BK. (2008) Withdrawal of analgesic medication for chronic low-back pain patients: improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. Am J Phys Med Rehabil;87(7): 527-36.

Currie J (2001) Best Practices Treatment and Rehabilitation for Women with Substance Use Problems. Health Canada, Ottawa

Cushman P, Jr. (1978) Methadone maintenance: long-term follow-up of detoxified patients. Ann N Y Acad Sci 311: 165-72

Cushman P, Jr. (1981) Detoxification after methadone maintenance treatment. Ann N Y Acad Sci 362: 217-30

Darke S, Ross J, Mills K, Teeson M, Williamson A, and Harvard A. Benzodiazepine use among heroin users: baseline use, current use and clinical outcome. Drug Alcohol Rv 2010; 29(3): 250-5.

Darke S, Duflou J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. Drug Alcohol Depnd. 2010:106(1):1-6.

Darke S, Duflou J, Tork M. Drugs and voilent death: comparative toxicology of moicide and non-substance toxicity suicide victoms. Addiction 2009 Jun; 104(6): 1000-1005.

Dashe JS, Jackson GL, Olscher DA, Zane EH, Wendel GD, Jr. (1998) Opioid detoxification in pregnancy. Obstet Gynecol 92: 854-8

Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD (2002) Relationship between maternal methadone dosage and neonatal withdrawal. Obstet Gynecol 100: 1244-9

Dean AJ, Bell J, Mascord DJ, Parker G, Christie MJ (2002) A randomised, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. J Affect Disord 72: 85-90

Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L (2009) Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend 105: 9-15

DeMaria PA, Sterling R, Weinstein SP. The effect of stimulant and sedative use on treatment outcome of patients admitted to methadone maintenance treatment. Am J Addict. 2000 Spring; 9(2): 145-53.

Department of Health (England) (2007) Drug Misuse and Dependence: UK Guidelines on Clinical Managment. In: Department of Health (England) (ed), London

Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN (2009) Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ 181: 891-6

Doberczak TM, Kandall SR, Friedmann P (1993) Relationship between maternal methadone dosage, maternal-neonatal methadone levels, and neonatal withdrawal. Obstet Gynecol 81: 936-40

Dole VP, Nyswander M (1965) A Medical Treatment for Diacetylmorphine (Heroin) Addiction. A Clinical Trial with Methadone Hydrochloride. JAMA 193: 646-50

Dole VP, Nyswander ME (1966) Rehabilitation of heroin addicts after blockade with methadone. N Y State J Med 66: 2011-7

Doverty M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, Ling W (2001) Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. Pain 93: 155-63

Drozdick J, 3rd, Berghella V, Hill M, Kaltenbach K (2002) Methadone trough levels in pregnancy. Am J Obstet Gynecol 187: 1184-8

Drucker E, Rice S, Ganse G, Kegley J, Bonuck K, Tuchman E (2007) The Lancaster Office Based Opiate Treatment Program: A Case Study and Prototype for Community Physicians and Pharmacists Providing Methadone Maintenance Treatment in the United States. Addictive Disorders & Their Treatment 6: 121-135

Eap CB, Buclin T, Baumann P (2002) Interindividual variability of the clinical pharmacokinetics of methadone. Implications for the treamtnet of opioid dependence. Clinical Pharamcokinetics 41(14): 1153-1193.

Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz JM, Perrier A, Dayer P, Desmeules JA (2006) Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. Arch Intern Med 166: 1280-7

Elkader AK, Brands B, Dunn E, Selby P, Sproule BA (2009) Major depressive disorder and patient satisfaction in relation to methadone pharmacokinetics and pharmacodynamics in stabilized methadone maintenance patients. J Clin Psychopharmacol 29: 77-81

Ellwood DA, Sutherland P, Kent C, O'Connor M (1987) Maternal narcotic addiction: pregnancy outcome in patients managed by a specialized drug-dependency antenatal clinic. Aust N Z J Obstet Gynaecol 27: 92-8

Ernst E, Bartu A, Popescu A, Ileutt KF, Hansson R, Plumley N (2002) Methadone-related deaths in Western Australia 1993-99. Aust N Z J Public Health 26: 364-70

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P (2003) Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev: CD002208

Fairbank JA, Dunteman GH, Condelli WS (1993) Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. Am J Drug Alcohol Abuse 19: 465-74

Fanoe S, Hvidt C, Ege P, Jensen GB (2007) Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. Heart 93: 1051-5

Fareed A, Vayalapalli S, Byrd-Sellers J, Casarella J, Drexler K, Amar R, Smith-Cox J, Lutchman TS (2010) Onsite QTc interval screening for patients in methadone maintenance treatment. J Addict Dis 29: 15-22

Farrell M, Neeleman J, Gossop M, Griffiths P, Buning E, Finch E, Strang J (1996) A Review of the Legislation, Regulation and Delivery of Methadone in 12 Member States of the European Union. The European Commission, Brussels, Belgium

Fiellin DA, O'Connor PG, Chawarski M, Pakes JP, Pantalon MV, Schottenfeld RS (2001) Methadone maintenance in primary care: a randomized controlled trial. JAMA 286: 1724-31

Finnegan LP (1978) Management of pregnant drug-dependent women. Ann N Y Acad Sci 311: 135-46

Finnegan LP (1991) Treatment issues for opioid-dependent women during the perinatal period. J Psychoactive Drugs 23: 191-201

Finnegan LP, Kaltenbach K (1992) Neonatal abstienence syndrome. In: Hoekelman, Nelson (eds) Primary Pediatric Care. Mosby Yearbook Inc., St. Louis

Finnegan LP, Kron RE, Connaughton JF, Emich JP (1975) Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm 12: 19-32

Firoz S, Carlson G (2004) Characteristics and treatment outcome of older methadone-maintenance patients. Am J Geriatr Psychiatry 12: 539-41

Fischer B, Rehm J, Brissette S, Brochu S, Bruneau J, El-Guebaly N, Noel L, Tyndall M, Wild C, Mun P, Baliunas D (2005) Illicit opioid use in Canada: comparing social, health, and drug use characteristics of untreated users in five cities (OPICAN study). J Urban Health 82: 250-66

Fricker HS, Segal S (1978) Narcotic addiction, pregnancy, and the newborn. Am J Dis Child 132: 360-6

Friedman R, Kamel I, Perez C, Hamada A (2003) Severe intraoperative hypertension and opioid-resistant postoperative pain in a methadone-treated patient. J Pain 4: 289-90

Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K (2003) Strabismus in infants of opiate-dependent mothers. Acta Paediatr 92: 379-85

Girela E, Villanueva E, Hernandez-Cueto C, Luna JD (1994) Comparison of the CAGE questionnaire versus some biochemical markers in the diagnosis of alcoholism. Alcohol Alcohol 29: 337-43

Girgis G (2009) Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med 151: 217-8; author reply 218-9

Glatstein MM, Garcia-Bournissen F, Finkelstein Y, Koren G (2008) Methadone exposure during lactation. Can Fam Physician 54: 1689-90

Gossop M, Green L, Phillips G, Bradley B (1989) Lapse, relapse and survival among opiate addicts after treatment. A prospective follow-up study. Br J Psychiatry 154: 348-53

Gossop M, Green L, Phillips G, Bradley B (1990) Factors predicting outcome among opiate addicts after treatment. Br J Clin Psychol 29 (Pt 2): 209-16

Gossop M, Stewart D, Marsden J (2006) Effectiveness of drug and alcohol counselling during methadone treatment: content, frequency, and duration of counselling and association with substance use outcomes. Addiction 101: 404-12

Green L, Gossop M (1988) Effects of information on the opiate withdrawal syndrome. Br J Addict 83: 305-9

Greenwald MK, Schuh KJ, Stine SM (2003) Transferring methadone-maintained outpatients to the buprenorphine sublingual tablet: a preliminary study. Am J Addict 12: 365-74

Grochow L, Sheidler V, Grossman S, Green L, Enterline J (1989) Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. Pain 38: 151-7

Gunne LM, Gronbladh L (1981) The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend 7: 249-56

Gutstein, HB and Akil, H. (2006) Opioid Analgesics. In: Goodman and Gilman's Pharmacological Basis of Therapeutics. 11th edition. Brunton L, Lazo JS, and Marker, KI (eds). McGraw-Hill, New York.

Hans SL (1989) Developmental consequences of prenatal exposure to methadone. Ann N Y Acad Sci 562: 195-207

Harding-Pink D (1993) Methadone: one person's maintenance dose is another's poison. Lancet 341: 665-6

Harris KA, Arnsten JH, Litwin AH (2010) Successful Integration of Hepatitis C Evaluation and Treatment Services With Methadone Maintenance. J Addict Med 4: 20-26

Health Canada (2002) Best Practices: Methadone Maintenance Treatment. Minister of Public Works and Government Services, Ottawa

Hillebrand J, Marsden J, Finch E, Strang J (2001) Excessive alcohol consumption and drinking expectations among clients in methadone maintenance. J Subst Abuse Treat 21: 155-60

Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD (2007) Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. Pain Med 8(1):8-16.

Hubbard RL, Craddock SG, Anderson J (2003) Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). J Subst Abuse Treat 25: 125-34

Hulse GK, Milne E, English DR, Holman CD (1997) The relationship between maternal use of heroin and methadone and infant birth weight. Addiction 92: 1571-9

Hulse GK, Milne E, English DR, Holman CD (1998) Assessing the relationship between maternal opiate use and neonatal mortality. Addiction 93: 1033-42

Hunt RW, Tzioumi D, Collins E, Jeffery HE (2008) Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev 84: 29-35

Iguchi MY, Stitzer ML, Bigelow GE, Liebson IA (1988) Contingency management in methadone maintenance: effects of reinforcing and aversive consequences on illicit polydrug use. Drug Alcohol Depend 22: 1-7

Jansson LM, Dipietro JA, Velez M, Elko A, Knauer H, Kivlighan KT (2009) Maternal methadone dosing schedule and fetal neurobehaviour. J Matern Fetal Neonatal Med 22: 29-35

Jansson LM, Velez M, Harrow C (2004) Methadone maintenance and lactation: a review of the literature and current management guidelines. J Hum Lact 20: 62-71

Jarvis MA, Schnoll SH (1994) Methadone treatment during pregnancy. J Psychoactive Drugs 26: 155-61

Jarvis MA, Wu-Pong S, Kniseley JS, Schnoll SH (1999) Alterations in methadone metabolism during late pregnancy. J Addict Dis 18: 51-61

Jones HE, O'Grady KE, Malfi D, Tuten M (2008) Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict 17: 372-86

Justo D, Gal-Oz A, Paran Y, Goldin Y, Zeltser D (2006) Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. Addiction 101: 1333-8

Kaltenbach K, Comfort ML (1997) Methadone maintenance of greater than 80 mg during pregnancy. NIDA Research Monograph 174: 128

Kaltenbach K, Finnegan LP (1986) Neonatal abstinence syndrome, pharmacotherapy and developmental outcome. Neurobehav Toxicol Teratol 8: 353-5

Kaltenbach K, Finnegan LP (1987) Perinatal and developmental outcome of infants exposed to methadone in-utero. Neurotoxicol Teratol 9: 311-3

Kaltenback K, Finnegan LP (1992) Methadone maintenance during pregnancy: Implications for perinatal and developmental outcome. In: Sonderegger TB (ed) Perinatal substance abuse: Research findings and clinical implications. Johns Hopkins University Press, Baltimore

Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman A, Lowinson J (1977) The narcotic-dependent mother: fetal and neonatal consequences. Early Hum Dev 1: 159-69

Kandall SR, Doberczak TM, Jantunen M, Stein J (1999) The methadone-maintained pregnancy. Clin Perinatol 26: 173-83

Kanof PD, Aronson MJ, Ness R (1993) Organic mood syndrome associated with detoxification from methadone maintenance. Am J Psychiatry 150: 423-8

Kellogg S, Melia D, Khuri E, Lin A, Ho A, Kreek MJ. Adolescent and young adult heroin patients: drug use and success in methadone maintenance treatment. J Addict Dis. 2006; 25(3): 15-25.

Kienbaum P, Thurauf N, Michel MC, Scherbaum N, Gastpar M, Peters J (1998) Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. Anesthesiology 88: 1154-61

King VL, Stoller KB, Hayes M, Umbricht A, Currens M, Kidorf MS, Carter JA, Schwartz R, Brooner RK (2002) A multicenter randomized evaluation of methadone medical maintenance. Drug Alcohol Depend 65: 137-48

Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady KE (2009) A randomized clinical trial of methadone maintenance for prisoners: results at 12 months postrelease. J Subst Abuse Treat 37: 277-85

Kletter E (2003) Counseling as an intervention for the cocaine-abusing methadone maintenance patient. J Psychoactive Drugs 35: 271-7

Kraft MK, Rothbard AB, Hadley TR, McLellan AT, Asch DA (1997) Are supplementary services provided during methadone maintenance really cost-effective? Am J Psychiatry 154: 1214-9

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC (2009) QTc interval screening in methadone treatment. Ann Intern Med 150: 387-95

Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M (1980) Methadone use in patients with chronic renal disease. Drug Alcohol Depend 5: 197-205

Lambert M, 1992 Psychotherapy outcome research: Implications for integrative and eclectic therapists. In J.C. Norcross & M.R. Goldfried (Eds.) Handbook of psychotherapy integration. New York: Basic.

Levin FR, Fischman MW, Connerney I, Foltin RW (1997) A protocol to switch high-dose, methadone-maintained subjects to buprenorphine. Am J Addict 6: 105-16

Lewis D, Bellis M (2001) General practice or drug clinic for methadone maintenance? A controlled comparison of treatment outcomes. Int J Drug Policy 12: 81-89

Lifschitz MH, Wilson GS, Smith EO, Desmond MM (1985) Factors affecting head growth and intellectual function in children of drug addicts. Pediatrics 75: 269-74

Ling W, Wesson DR, Charuvastra C, Klett CJ (1996) A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry 53: 401-7

Little BB, Snell LM, Klein VR, Gilstrap LC, 3rd, Knoll KA, Breckenridge JD (1990) Maternal and fetal effects of heroin addiction during pregnancy. J Reprod Med 35: 159-62

Lovecchio F, Pizon A, Riley B, Sami A, D'Incognito, C (2007) Onset of symptoms after methadone overdose. Am J Emerg Med, 25(1): 57-59.

Lowinson JH, Marion I, Joseph H, Langrod J, Salsitz EA, Payte JT, and Dole VP (2006) Methadone Maintenance. In: Substance Abuse: A Comprehensive Textbook. Fourth edition. Lowinson JH, Ruiz P, Millman RB, and Langrod JG (eds). Lippincott Williams & Wilkins, Philadelphia.

Luty J, Nikolaou V, Bearn J (2003) Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat 24: 363-7

Maas U, Kattner E, Weingart-Jesse B, Schafer A, Obladen M (1990) Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. J Perinat Med 18: 111-8

Magura S, Rosenblum A (2001) Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. Mt Sinai J Med 68: 62-74

Man LH, Best D, Gossop M, Stillwell G, Strang J. Relationship between prescribing and risk of opioid overdose among drug users in and out of maintenance treatment. Eur Addict Res. 2004; 10(1): 35-40.

Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, Brooklyn J (2005) Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Arch Gen Psychiatry 62: 1157-64

Martin DJ, Garske JP, Davis MK (2000) Relation of the therapeutic alliance with outcome and other variables: a meta-analytic review. J Consult Clin Psychol 68: 438-50

Martin TL, Woodall KL, McLellan BA (2006) Fentanyl-related deaths in Ontario, Canada: toxicological findings and circumstances of death in 112 cases (2002-2004). J Anal Toxicol 30: 603-10

Mason BJ, Kocsis JH, Melia D, Khuri ET, Sweeney J, Wells A, Borg L, Millman RB, Kreek MJ (1998) Psychiatric comorbidity in methadone maintained patients. J Addict Dis 17: 75-89

Mattick RP, Breen C, Kimber J, Davoli M (2009) Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev: CD002209

Mattick RP, Kimber J, Breen C, Davoli M (2008) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev: CD002207

Mayes LC, Carroll KM (1996) Neonatal withdrawal syndrome in infants exposed to cocaine and methadone. Subst Use Misuse 31: 241-53

McCann M, Rawson R, Obert J, Hasson A (1994) A Treatment of Opiate Addiction Using Methadone: A Counselor Manual. Center for Substance Abuse Treatment, Center for Substance Abuse Treatment

McCusker M (2001) Influence of hepatitis C status on alcohol consumption in opiate users in treatment. Addiction 96: 1007-14

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP (1993) The effects of psychosocial services in substance abuse treatment. JAMA 269: 1953-9

Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L, Villari P, Ficorella C, Gebbia V, Riina S, Casuccio A, Mangione S (2008) Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain 12: 1040-6

Merrill JO, Jackson TR, Schulman BA, Saxon AJ, Awan A, Kapitan S, Carney M, Brumback LC, Donovan D (2005) Methadone medical maintenance in primary care. An implementation evaluation. J Gen Intern Med 20: 344-9

Mikolaenko I, Robinson CA, Jr., Davis GG (2002) A review of methadone deaths in Jefferson County, Alabama. Am J Forensic Med Pathol 23: 299-304

Milby JB (1988) Methadone maintenance to abstinence. How many make it? J Nerv Ment Dis 176: 409-22

Milby JB, Gurwitch RH, Wiebe DJ, Ling W, McLellan AT, Woody GE (1986) Prevalence and diagnostic reliability of methadone maintenance detoxification fear. Am J Psychiatry 143: 739-43

Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ (2007) The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. J Pain Palliat Care Pharmacother 21: 5-16

Nelson LB, Ehrlich S, Calhoun JH, Matteucci T, Finnegan LP (1987) Occurrence of strabismus in infants born to drug-dependent women. Am J Dis Child 141: 175-8

Newman RG, Whitehill WB (1979) Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. Lancet 2: 485-8

NIDA (1999) Drug Misuse and DependenceL Guidelines on Clinical Management. National Institute on Drug Abuse Bethesda, MD

Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH (2010) Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996-2006. J Subst Abuse Treat 39: 22-31

Novick DM, Kreek MJ, Arns PA, Lau LL, Yancovitz SR, Gelb AM (1985) Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. Alcohol Clin Exp Res 9: 349-54

OCP Ontario College of Pharmacists (September 2010). Revised MMT and Dispensing Policy.

Olsen GD, Wendel HA, Livermore, JD, Leger RM, Lynn RK, Gerber N (1977) Clinical effects and pharamcokinetics of racemic methadone and its optical isomers. Clinical Pharmacology & Therapeutics 21(2):147-157.

Ontario Addiction Services Advisory Counsil (2000) Admission and Discharge Criteria for Ontario's Substance Abuse Services. Ontario Substance Abuse Bureau, Ministry of Health and Long-Term Care. Toronto

Ontario Select Committee on Mental Health and Addictions (2010) Final Report Navigating the Journey to Wellness. The Comprehensive Mental Health and Addictions Action Plan for Ontarians. Legislative Assembly of Ontario.

Pani PP, Pirastu R, Ricci A, Gessa GL (1996) Prohibition of take-home dosages: negative consequences on methadone maintenance treatment. Drug Alcohol Depend 41: 81-4

Peles E, Schreiber S, Adelson M. 15-Year survival and retention of pateints in a general hospital-affiliated methadone maintenance treatment (MMT) in Israel. Drug Alcohol Depend. 2010 Mar 1; 107(2-3): 141-8.

Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, Kress HG, Langford R, Likar R, Raffa RB, Sacerdote P (2008) Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 8: 287-313

Perrone J, De Roos F, Jayaraman S, Hollander JE (2001) Drug screening versus history in detection of substance use in ED psychiatric patients. Am J Emerg Med 19: 49-51

Petitjean S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, Ladewig D (2001) Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend 62: 97-104

Pimentel L, Mayo D (2008) Chronic methadone therapy complicated by torsades de pointes: a case report. J Emerg Med 34: 287-90

Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE (2010) Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. Addiction 105: 1616-24

Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL (1985) Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther 233: 1-6

Popova S, Rehm J, Fischer B (2006) An overview of illegal opioid use and health services utilization in Canada. Public Health 120: 320-8

Preston KL, Umbricht A, Epstein DH (2002) Abstinence reinforcement maintenance contingency and one-year follow-up. Drug Alcohol Depend 67: 125-37

Rabinowitz J, Cohen H, Tarrasch R, Kotler M (1997) Compliance to naltrexone treatment after ultra-rapid opiate detoxification: an open label naturalistic study. Drug Alcohol Depend 47: 77-86

Rajaratnam R, Sivesind D, Todman M, Roane D, Seewald R (2009) The aging methadone maintenance patient: treatment adjustment, long-term success, and quality of life. J Opioid Manag 5: 27-37

Rauck RL, Bookbinder SA, Bunker TR, Alftine CD, Gershon S, de Jong E, Negro-Vilar A, Ghalie R (2007) A randomized, open-label, multicenter trial comparing once-a-day AVINZA (morphine sulfate extended-release capsules) versus twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: improved physical functioning in the ACTION trial. J Opioid Manag 3: 35-43

Rementeria JL, Nunag NN (1973) Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. Am J Obstet Gynecol 116: 1152-6

Repchinsky C (2003) Compendium of Pharmaceuticals and Specialties: The Canadian Drug Reference for Health Professionals. Canadian Pharmacists Association, Ottawa, Ontario

Richman A, Perkins ME, Bihari B, Fishman JJ (1972) Entry into methadone maintenance programs: a follow-up study of New York City heroin users detoxified in 1961-1963. Am J Public Health 62: 1002-7

Ries RK, Dyck DG, Short R, Srebnik D, Snowden M, Comtois KA (2002) Use of case manager ratings and weekly urine toxicology tests among outpatients with dual diagnoses. Psychiatr Serv 53: 764-6

Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK (2003) Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA 289: 2370-8

Schmitz JM, Rhoades HM, Elk R, Creson D, Hussein I, Grabowski J (1998) Medication take-home doses and contingency management. Exp Clin Psychopharmacol 6: 162-8

Schottenfeld R, Pakes J, Kosten T. (1998) Prognostic factors in Buprenorpine versus Methadone maintained patients. J Nerv Ment Dis 186(1):35-43.[MEDLINE: 1998118328}

Schreiber S, Peles E, Adelson M (2008) Association between improvement in depression, reduced benzodiazepine (BDZ) abuse, and increased psychotropic medication use in methadone maintenance treatment (MMT) patients. Drug Alcohol Depend 92: 79-85

Schroeder JR, Schmittner JP, Epstein DH, Preston KL (2005) Adverse events among patients in a behavioral treatment trial for heroin and cocaine dependence: effects of age, race, and gender. Drug Alcohol Depend 80: 45-51

Scott CC, Robbins EB, Chen KK (1948) Pharmacological comparison of the optical isomers of methadone. Journal of Pharmacology and Experimental Therapeutics 93:282-286.

Senay EC, Dorus W, Goldberg F, Thornton W (1977) Withdrawal from methadone maintenance. Rate of withdrawal and expectation. Arch Gen Psychiatry 34: 361-7

Sims SA, Snow LA, Porucznik CA (2007) Surveillance of methadone-related adverse drug events using multiple public health data sources. J Biomed Inform 40: 382-9

Sproule B, Brands B, Li S, Catz-Biro L (2009) Changing patterns in opioid addiction: characterizing users of oxycodone and other opioids. Can Fam Physician 55: 68-9, 69 e1-5

Srivastava A, Kahan M (2006) Methadone induction doses: are our current practices safe? J Addict Dis 25: 5-13

Srivastava A, Kahan M, Ross S (2008) The effect of methadone maintenance treatment on alcohol consumption: a systematic review. J Subst Abuse Treat 34: 215-23

Stern R (1966) The pregnant addict. A study of 66 case histories, 1950-1959. Am J Obstet Gynecol 94: 253-7

Stimmel B, Goldberg J, Cohen M, Rotkopf E (1978) Detoxification from methadone maintenance: risk factors associated with relapse to narcotic use. Ann N Y Acad Sci 311: 173-80

Stimmel B, Goldberg J, Reisman A, Murphy RJ, Teets K (1982) Fetal outcome in narcotic-dependent women: the importance of the type of maternal narcotic used. Am J Drug Alcohol Abuse 9: 383-95

Stitzer ML, Iguchi MY, Felch LJ (1992) Contingent take-home incentive: effects on drug use of methadone maintenance patients. J Consult Clin Psychol 60: 927-34

Strain EC, Stitzer ML, Liebson IA, Bigelow GE (1993) Dose-response effects of methadone in the treatment of opioid dependence. Ann Intern Med 119: 23-7

Strike CJ, Gnam W, Urbanoski K, Fischer B, Marsh DC, Millson M (2005) Factors predicting 2-year retention in methadone maintenance treatment for opioid dependence. Addict Behav 30: 1025-8

Subramaniam GA, Fishman MJ, Woody G (2009) Treatment of opioid-dependent adolescents and young adults with buprenorphine. Curr Psychiatry Rep 11: 360-3

Swift RM, Dudley M, DePetrillo P, Camara P, Griffiths W (1989) Altered methadone pharmacokinetics in pregnancy: implications for dosing. J Subst Abuse 1: 453-60

Szabo G, Wands JR, Eken A, Osna NA, Weinman SA, Machida K, Joe Wang H (2010) Alcohol and hepatitis C virus--interactions in immune dysfunctions and liver damage. Alcohol Clin Exp Res 34: 1675-86

Tschakovsky K (2009) Methadone Maintenance Treatment: Best Practices in Case Managment. Centre for Addiction and Mental Health, Toronto

Tuchman E (2007) Exploring the prevalence of menopause symptoms in midlife women in methadone maintenance treatment. Soc Work Health Care 45: 43-62

Tuchman E (2010) Menopause symptom attribution among midlife women in methadone treatment. Soc Work Health Care 49: 53-67

Uhlmann S, Milloy MJ, Kerr T, Zhang R, Guillemi S, Marsh D, Hogg RS, Montaner JS, Wood E (2010) Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. Addiction 105: 907-13

Unnithan S, Gossop M, Strang J (1992) Factors associated with relapse among opiate addicts in an out-patient detoxification programme. Br J Psychiatry 161: 654-7

Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ (2010) A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev 30: 155-66

Villano CL, Rosenblum A, Magura S, Fong C (2002) Improving treatment engagement and outcomes for cocaine-using methadone patients. Am J Drug Alcohol Abuse 28: 213-30

Vucinovic M, Roje D, Vucinovic Z, Capkun V, Bucat M, Banovic I (2008) Maternal and neonatal effects of substance abuse during pregnancy: our ten-year experience. Yonsei Med J 49: 705-13

Washton AM, Pottash AC, Gold MS (1984) Naltrexone in addicted business executives and physicians. J Clin Psychiatry 45: 39-41

Wasserman DA, Korcha R, Havassy BE, Hall SM (1999) Detection of illicit opioid and cocaine use in methadone maintenance treatment. Am J Drug Alcohol Abuse 25: 561-71

Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC (2007) QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med 167: 2469-75

WHO (2009) Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. World Health Organization, Geneva

Wilson GS, Desmond MM, Wait RB (1981) Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: health, developmental, and social implications. J Pediatr 98: 716-22

Wittmann BK, Segal S (1991) A comparison of the effects of single- and split-dose methadone administration on the fetus: ultrasound evaluation. Int J Addict 26: 213-8

Wolff K (2002) Characterization of methadone overdose: clinical considerations and the scientific evidence. Ther Drug Monit 24: 457-70

Wolff K, Boys A, Rostami-Hodjegan A, Hay A, Raistrick D (2005) Changes to methadone clearance during pregnancy. Eur J Clin Pharmacol 61: 763-8

Wong T, Lee SS (2006) Hepatitis C: a review for primary care physicians. CMAJ 174: 649-59

Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, Patkar A, Publicker M, McCain K, Potter JS, Forman R, Vetter V, McNicholas L, Blaine J, Lynch KG, Fudala P (2008) Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA 300: 2003-11

Yancovitz SR, Des Jarlais DC, Peyser NP, Drew E, Friedmann P, Trigg HL, Robinson JW (1991) A randomized trial of an interim methadone maintenance clinic. Am J Public Health 81: 1185-91

Zador D, Sunjic S (2000) Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. Addiction 95: 77-84