This is Exhibit A referred to in the affidavit of Dr. David Marsh sworn before me, this 25th day of May 20 15

A COMMISSIONER FOR TAKING AFFIDAVITS

David C. Marsh, MD, CCSAM

Northern Ontario School of Medicine
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Current Positions

Deputy Dean & Associate Dean, Community Engagement
Northern Ontario School of Medicine

Professor, Clinical Sciences, Northern Ontario School of Medicine
Laurentian University and Lakehead University

Chief Medical Director
Ontario Addiction Treatment Centres

CARBC Collaborating Scientist
Centre for Addictions Research of BC

Education

American Board of Addiction Medicine
Diplomat, May 2009

Medical Council of Canada
Licentiate, *June 2006*

International Society of Addiction Medicine
Certificant, November 2005

American Society of Addiction Medicine
Certificant, April, 2005

Canadian Society of Addiction Medicine
Certificant, November 2000

University of Toronto
Rotating Internship, 1992 - 1993
Mt. Sinai Hospital

Memorial University of Newfoundland
MD, 1984 - 1992
Dean's List for Med I & Med III

Memorial University of Newfoundland
PhD candidate, 1986 - 1990
PhD candidate in Neuroscience /Pharmacology
(did not complete thesis)
Thesis title: *Pharmacology of the Rat Oesophageal Myenteric Plexus*

Awards

Physician Achievement Award
2014 OMA Section on Addiction Medicine

Nyswander-Dole (Marie) Award
American Association for the Treatment of Opiate Dependence 2004

The College of Physicians and Surgeons of Ontario
2002 Council Award

Clinical Experience

Vancouver Coastal Health and Providence Health Care
Physician Leader, Addiction Medicine, 2004 – 2010
Addiction Medicine practice within an integrated multi-disciplinary team based at the NAOMI clinic, the Immunodeficiency Clinic and Acute Care Inpatient units at St. Paul's Hospital and Mount Saint Joseph's Hospital including addiction medicine consultations, complex pain management in the face of addiction, methadone maintenance treatment, outpatient withdrawal management and focussed primary care.

Addiction Research Foundation and Centre for Addiction and Mental Health
Addiction Medicine Consultant, 1995 - 2003

Outpatient and residential Addiction Medicine practice focussed on treatment of intoxication and withdrawal from alcohol, benzodiazepines, barbiturates and opiates, and on psychotherapeutic and pharmacological measures to support abstinence including opioid agonist therapy.

Wellesley Central Hospital
Consultant, 1996 - 1999
Providing staff training and education in the area of addictions and consultation support for inpatients admitted to the general medical and human immunodeficiency virus services.

Mental Health and Addictions Associates
Physician Psychotherapist, 1994 - 1996
Full-Time GP-Psychotherapy practise concentrating on time-limited psychodynamic therapy for depression, anxiety, grief and individuals affected by HIV.

Management Experience

Northern Ontario School of Medicine
Deputy Dean, 2015 - present

- Deputy Dean is responsible for leading whole-school academic program developments by enabling, facilitating, and coordinating cross-portfolio collaborative initiatives which are consistent with the NOSM Strategic Plan and determined by the Executive Group. The Deputy Dean may assume the Dean's responsibilities during the Dean's absence. In addition,

Associate Dean, Community Engagement, 2010 – present

- Responsible for a range of programs critical to the implementation of the social accountability mandate of the school including: Admissions, Francophone Affairs, Aboriginal Affairs, Integrated Clinical Learning (including Health Professional training programs in Occupational Therapy, Physiotherapy, Dietetics and Physician Assistants) and Clinical Placements and Electives (including housing for learners placed away from home for 6 months or less and processing of all elective placements for students and residents from other medical schools nationally and internationally).

Senior Associate Dean, East Campus, 2011 – present

- Represents school in relationships with key community partners in North-Eastern Ontario including Laurentian University, Academic Health Science Centres and Teaching Hospitals in Sudbury, North Bay, Sault St. Marie, Timmins and other identified key external stakeholders for the school.

Interim Associate Dean, Undergraduate Medical Education 2013 – 2014

- Reporting to the Dean, the Associate Dean, Undergraduate Medical Education (UME), is responsible to the Dean for all aspects of planning, development, implementation, management and program evaluation of the four year undergraduate medical education program leading to award of the MD degree.

Ontario Addiction Treatment Centres
Chief Medical Director, 2014 - present

- Reporting to the Co-Chief Executive Officers of a organizations with over 55 clinics, 50 physicians 250 staff and 15,0000 patients receiving opioid agonist treatment, the Chief Medical Director (CMD) works closely with both administrative staff and members of the medical staff and its leadership to maintain the high quality of medical care and to promote medical staff participation in furthering the mission of the organization
- The CMD assists the medical staff in formulating standards of care and strategic direction for quality, facilitates communication between the medical staff and administration, and ensures positive medical staff relations. The CMD works to align medical staff goals with those of the Administration and ensures compliance with all quality, legal, and regulatory requirements.

Vancouver Coast Health and Providence Health Care
Physician Leader, Addiction Medicine, 2004 - 2010

- Responsible for clinical leadership and strategic planning for addiction services across all geographic and functional

components of a complex acute-care and community-based health care organization. Lead integration of addiction care into Mental Health, Acute Care, Continuing Care and Primary Care service delivery areas. Within this role I also had the following responsibilities:

Medical Director, Addiction, HIV/AID Services and Aboriginal Health, Vancouver Community

- Co-management of direct and contracted community services with an annual budget in excess of $60 million
- Establishment of physician human resource planning and management across addiction medicine, HIV care and Aboriginal health
- Development and implementation of quality management and quality assurance processes including physician peer assessments and broadly based program evaluation
- Responsible Physician for Canada's first supervised injection site

Division Head, Addiction Medicine, Department of Family and Community Medicine, St. Paul's Hospital

- Planning of addiction care within the acute care setting for Providence Health Care and the integration of this care between inpatient, emergency and community settings

Centre for Addiction and Mental Health
Clinical Director, Addiction Medicine, 1998- 2003
Responsible for the clinical, research and training elements of the Addiction Medicine Program across all four sites of the Centre for Addiction and Mental Health. Key responsibilities and achievements include the following:

- Managing a budget of over $3 million and more than 100 staff (including 11 physicians)
- Leading the integration of services across two sites with different treatment philosophies for the first 5 years after the hospital merger forming CAMH including integration of harm reduction and abstinence-based services
- Through partnership with external agencies (such as the CPSO) leading the expansion of Methadone Maintenance Treatment (MMT) across Ontario with 10-fold increase in number of patients in treatment, evidence-based guidelines, training manuals for physicians, pharmacists and counselors, and a peer-assessment process for physicians
- Developing and evaluating an integrated spectrum of withdrawal management services including outpatient, residential non-medical and medical settings
- Served as Vice-Chair of the Medical Advisory Committee (1998-2003) and Co-Chair of the Client-Patient Information Implementation Committee (1998-2003)
- Chair of Infection Control Committee (1998-2003) including development of Infection Control Manual for CAMH and co-leading response to SARS outbreaks in spring 2003 with Physician-in-Chief

Addiction Research Foundation
Clinical Chief, Pharmacotherapy, 1996 - 1998
While administratively responsible for the Addiction Medicine Clinic, Opiate Clinic, Non-medical Withdrawal Management Service and Pharmacy was integral in the following:

- Managing a budget of over $2 million and more than 40 staff (including 8 physicians)
- Implementing cost-recovery for outpatient pharmacy services which resulted in reducing the actual cost to the organisation for Pharmacy Services by more than $250,000 and within 6 months of initiation cost recovery was ahead of budget projections
- Developed and implemented a new physician payment system that resulted in more predictable budgeting, increased incentive for physicians to increase client load, decreased cost to the organisation by more than $100,000, and stable net physician remuneration.

Successfully completed the following management training courses:

- Time Management, York University, October, 1997
- Project Management, York University, May, 1997
- Management I: The New Managers Course, York University, April, 1997
- Physician Management Institutes I, II, III and IV, CMA, April - May, 1997

Previous Academic Positions

University of British Columbia
Clinical Professor, School of Population and Public Health, Faculty of Medicine, 2010 – 2011

Clinical Associate Professor, Health Care and Epidemiology, Faculty of Medicine, 2004 - 2010
Founding Fellow, Institute of Mental Health, Faculty of Medicine, 2007 - 2010

University of Victoria
Senior Research Fellow, Centre for Addiction Research British Columbia, 2007-2009+

Providence Health Care
Research Scientist, Centre for Health Evaluation and Outcome Sciences, 2004-2010

University of Toronto
Assistant Professor, Department of Psychiatry and Department of Family and Community Medicine, Faculty of Medicine, 1997 - 2003

Memorial University of Newfoundland
Lecturer, 1986 – 1991

Teaching – Graduate Students

Post-doc: Joe Eibl, Northern Ontario School of Medicine, July 2013 to present

Post-doc: Behdin Nowrouzi, Northern Ontario School of Medicine, July 2013 to 2014

Supervisor PhD Thesis: Neghesti Gebru, Laurentian University, September 2011 to 2013

Supervisor: Nathan Kolla, Masters of Science, Sociology, University of Toronto, February 2002 to August 2003

Supervisor: Ajay Puri, Masters of Health Science Administration, University of British Columbia, September 2003 to August 2005

Project Supervisor: Denielle Elliott, Ph.D. Student, Medical Anthropology, Simon Fraser University, September 2004 to December 2005

Project Supervisor: Sarah Fielden, Ph.D. Student, Health Care Epidemiology, University of British Columbia, September 2005 to August 2006

Conference and Meeting Planning

Canadian Recruit and Retain Conference
Thunder Bay, ON, January 15 – 17, 2014
Conference Planning Committee

Rendez-Vous 2012
Thunder Bay, ON October 9 – 14, 2012
Conference Planning Committee

2012 Annual Meeting & Scientific Conference, Canadian Society of Addiction Medicine
Toronto, ON September 20 – 22, 2012

International Society of Addiction Medicine Annual Conference
Calgary, AB, September 23 – 26, 2009
Conference Committee
20th Annual Scientific Conference, Canadian Society of Addiction Medicine
Vancouver, BC, October 30 to November 1, 2008
Chair, Conference Committee

1ST Global Conference on Methamphetamine

Prague, Czech Republic, September 15 – 17, 2008
Executive Program Committee

2nd Bi-Annual Issues of Substance Conference
Canadian Centre on Substance Abuse
Edmonton, AB, November 25 to November 28, 2007
Conference Planning Committee

19th Annual Scientific Conference, Canadian Society of Addiction Medicine
Ottawa, ON, Oct. 10 to Oct. 14, 2007
Conference Committee

18th International Conference on the Reduction of Drug-Related Harm
Warsaw, Poland, May 13 to May 17, 2007
International Advisory Committee Member

Canadian Buprenorphine Core Training Program
Saskatoon, SK, October 15, 2006
Course Director

18th Annual Scientific Conference, Canadian Society of Addiction Medicine
Saskatoon, SK, Oct. 11 – Oct. 14, 2006
Conference Committee

17th International Conference on the Reduction of Drug-Related Harm
Vancouver, BC, April 30 – May 4, 2006
Conference Program Co-Chair

Canadian Buprenorphine Core Training Program
Vancouver, BC, October 24, 2005
Course Director

17th Annual Scientific Conference, Canadian Society of Addiction Medicine
Vancouver, BC, Oct. 20 –Oct. 23, 2005
Conference Chair

14th Annual Canadian Conference on HIV/AIDS Research, Canadian Association for HIV Research
Vancouver, BC, May 12 – May 15, 2005
Clinical Track Program Co-Chair

Western Canada Summit on Methamphetamine, Vancouver Coastal Health
Vancouver, BC, Nov. 15 – Nov. 17, 2004
Conference Planning Committee Member

16th Annual Scientific Conference, Canadian Society of Addiction Medicine
Toronto, ON, Oct. 21 – Oct. 24, 2004
Conference Committee and Program Committee Member

Research Grants and Awards

Name of Project: Evaluating the Impact of Benzodiazepine Use in Patients Enrolled in Opioid Agonist Therapy (submitted)
PI: D.C. Marsh Co-Investigators: J. Eibl
Start Date: 2014 End Date: 2015
Granting Agency: NOAMA AFP Innovation Fund
Total Amount of Grant: $ 50,000 CAN

Name of Project: Identifying Clinical Factors Which Contribute to Improved Retention for Patients Undergoing Opioid Agonist Therapy in Northern Regions of Ontario
PI: D.C. Marsh Co-Investigators: J. Eibl
Start Date: 2014 End Date: 2015
Granting Agency: NOAMA Clinical Innovation Opportunities Fund
Total Amount of Grant: $ 50,000 CAN

Name of Project: Canadian HIV Observational Cohort (CANOC) Collaborative Research Centre
PI: T. Antoniou, A.M. Bayoumi, A.N. Burchell, C.L. Cooper, R.S. Hogg, M.W. Hull, M. Warwick, D.V. Kelly, M.B. Klein, M.R. Loutfy, N.N. Machouf J.S.G. Montaner, B.P. Nosyk, J.M. Raboud, S.E. Sanche, C.M. Tsoukas, A.C.H. Wong
Co-Investigators: A. Cescon, M. Cotterchio, C.H. Goldsmith, A. Guillemi, R.P. Harrigan, M. Harris, S.R. Hosein, S.E.I. Johnston, C. Kendall C.E. Liddy, V.D. Lima, D.C. Marsh, D.M. Moore, S.E. Patterson, P. Phillips A.R. Rachlis, S.B. Rourke, H. Samji B. Trottier, M.A. Wainberg, S.L. Walmsley
Start Date: 2014 End Date: 2019
Granting Agency: Canadian Institutes of health Research (CIHR)
Total Amount of Grant: $ 454,492.00 CAN

Name of Project: Leveraging Clinical and Health Systems Data to Evaluate the Efficacy of Telehealth Delivered Addiction Therapy in the Province of Ontario
PI: D.C. Marsh Co-Investigators: J. Eibl
Start Date: 2014 End Date: 2015
Granting Agency: NOAMA Clinical Innovation Opportunities Fund
Total Amount of Grant: $ 50,000 CAN

Name of Project: Impact of HIV on aging-related comorbidities among key affected populations across Canada
PI: A.N. Burchell, C.L. Cooper, R.S. Hogg, M.B. Klein, M.R. Loutfy, N.N. Machouf, J.S.G. Montaner, J.M. Raboud, S.E. Sanche, C.M. Tsoukas,
Co-Investigators: T. Antoniou, A. Cescon, C.H. Goldsmith, S.A. Guillemi, M. Harris, M.W. Hull, V.D. Lima, D.C. Marsh, P. Phillips, A.R. Rachlis, S.B. Rourke, H. Samji, M.J. Smieja, S.L. Walmsley, A. Wong,
Start Date: 2014 End Date: 2017
Granting Agency: Canadian Institutes of Health Research (CIHR)
Total Amount of Grant: $ 150,000 CAN

Name of Project: Evaluation Factors that Lead to Successful Integration in the Labour Force among Patients Suffering from Opioid Addiction.
PI: D.C. Marsh Co-Investigators: J. Eibl
Start Date: 2013 End Date: 2014
Granting Agency: MTCU Ontario Human Capital Innovation Fund
Total Amount of Grant: $ 50,000 CAN

Name of Project: Evaluating the Efficacy of Opioid Agonist Therapy (OAT) in Rural Versus Urban Regions of Ontario.
PI: D.C. Marsh Co-Investigators: J. Eibl

Start Date: 2013 End Date: 2014
Granting Agency: NOAMA Clinical Innovation Fund
Total Amount of Grant: $ 50,000 CAN

Name of Project: Canadian Interprofessional Health Leadership Collaborative (CIHLC)
PI: S. Verma, M. Tassone Co-Investigators: L. Bainbridge, S. Berry, E. Careau, D.C. Marsh, M. Paterson
Start Date: April 2012 End Date: March 2015
Granting Agency: Ministry of Health and Long-Term Care
Total Amount of Grant: $2,738,400 CAN

Name of Project: Five views on a journey: Developing a systems model of treatment and care for mental health, substance use and violence problems
PI: K. Graham, S.L. Wells Co-Investigators: D. George, N. Medulun Burke, R. Moore, M.A. Oshea, M. Phinney, J.T. Rehm, B.R. Rush, S.L. Wells, H.L. Bullock, K.E. Irwin-Seguin, M.F. Jones, M. Lennox, C. Mitchell, A.P. Gouge, N. Kates, P.A. Kurdyak, D.C. Marsh, R.A. Mason, SAI Simpson, BB Toner.
Start Date: May 2012 End Date: April 2015
Granting Agency: Canadian Institutes of Health Research
Total Amount of Grant: $349,998 CAN

Name of Project: Study to Assess Longer-term Opioid medication Effectiveness (SALOME) : Multi-centre, double blind Randomized Controlled Trial comparing the efficacy of Diacetylmorphine vs. Hydromorphone for the treatment of long-term injection Opiate Users who do not benefit from available therapies
PI: R.M. Krausz, E. Oviedo-Joekes, A.H. Anis Co-Investigators: D.C. Marsh, B.P. Nosyk
N. Bansback, S. Brissette, J. Bruneau,
M.T. Schechter, C.G. Schutz
Start Date: April, 2010 End Date: March 2014
Granting Agency: Canadian Institutes of Health Research
Total Amount of Grant: $998,077 CAN

Name of Project: BC alcohol and other drug monitoring project: Implementation phase III
PI: T. Stockwell Co-Investigators: S. Macdonald, C. Duff, C. Chow, D.C. Marsh, J. Buxton, A. Tu, E. Saewyc, A. Smith, R. Corrado, I. Cohen.
Start Date: April, 2009 End Date: March, 2012
Granting Agency: BC Provincial Health Services Authority
Total Amount of Grant: $479,000 CAN

Name of Project: Drug normalization and stigma: Canada's experience with cannabis and tobacco
PI: P. Erickson Co-Investigators: M. Asbridge, S. Brochu, M. Cousineau, C. Duff, A. Hathaway, D.C. Marsh, C. Poulin
Start Date: April, 2007 End Date: March, 2011
Granting Agency: Social Sciences and Humanities Research Council
Total Amount of Grant: $116,895 CAN

Name of Project: Vancouver Multi-Disciplinary Collaboration of Injection Drug Use Researchers.
PI: T. Kerr & E. Wood Co-Investigators: D.C. Marsh, A.Palepu, J. Stoltz, S. Strathdee, M. Tyndall
Start Date: January 2006 End Date: December 2010
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $848,381 CAN

Name of Project: North American Opiate Medication Initiative (NAOMI): Multi-Centre Randomized Controlled Trial of Heroin-Assisted Therapy for Treatment Refractory Injection Opiate Users.
PI: M. Schechter Co-Investigators: D.C. Marsh, B. Fischer, J. Rehm, S. Brissette, P. Lauzon, C. Hankins, S. Brochu, M. O'Shaughnessy, A. Anis
Start Date: May, 2002 End Date: March, 2010
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $8,115,661 CAN

Name of Project: From Research to Action: Preventing HIV Infection and Other Harms among Injection Drug Users.
PI: E. Wood Co-Investigators: K.A.B. DeBeck, R.P. Harrigan, R.S. Hogg, T.H. Kerr, D. Macpherson, D.C. Marsh, J. Montaner, J.A. Shoveller, W.G. Small
Start Date: May, 2009 End Date: April, 2010
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $36, 500 CAN

Name of Project: An Evaluation of Long-Term Medical Outcomes Following Discontinuation of Methadone Maintenance Treatment
PI: A. Anis Co-Investigators: D.C. Marsh, B. Fischer, M. Schechter, Y. MacNab, B. Nosyk
Start Date: April 2008 End Date: March 2010
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $98,350 CAN

Name of Project: The CEDAR project: Exploring HIV and hepatitis C vulnerabilities among young aboriginal drug users in three Canadian Cities
PI: M. Schechter & P. Spittal Co-Investigators: C.P. Baylis, R.C. Callaghan, K. Craib, P. Joseph, P.A. Janssen, D.C. Marsh, A. Moniruzzaman, C.H. Sherlock, M.P. Teegee, C.M. Wayne, E.M. Yoshida
Start Date: October 1, 2006 End Date: September 30, 2009
Granting Agency: Canadian Institutes of Health Research
Total Amount of Grant: $1,300,392 CAN

Name of Project: Mental Health and Addiction Services and Policy Investigative Team.
PI: E. Goldner Co-Investigators: D. Maclean, A. Anis, W. Honer, W. Jones, J. Somers, C. Waddell, P. Waraich, J. Cutcliffe, V. Syme, T. Stockwell, J. Barker, A. Marr, J. Anderson, L. Arnold, P. Smith, E. Tovey, D. Duncan, A. Taft, M. Wharton, S. Ganesan, L. Howes, H. Hay, D.C. Marsh, B. Walther, P. Whiting, D. Burnham
Start Date: January 2006 End Date: December 2010
Granting Agency: Michael Smith Foundation for Health Research, Health Services & Policy Research Network Investigative Team Grant
Total amount of grant: $1,000,000 CAN

Name of Project: Substance use, stigma and normalization: the social transformation of drug use in modern society
PI: P. Erickson Co-Investigators: E. Adlaf, M. Asbridge, S. Brochu, M. Cousineau, C. Duff, A. Hathaway, D.C. Marsh, C. Poulin , B. Alexander, A. Anis, M.-A. Bertrand, L. Boellinger, N.T. Boyd, T. Decorte, C.A. Dell, L. Harrison, C.M.F. Jones, D.J. Korf, S.R. Lenton, E. Single, J.F.
Start Date: April 2005 End Date: March 2006

Granting Agency: Social Sciences and Humanities Research Council
Major Collaborative Research Initiative
Total Amount of Grant: $20,000 CAN

Name of Project: Detection and management of substance problems in emergency department patients
PI: J.R. Brubacher, R.A. Purssell Co-Investigators: R.B. Abu-Laban, D.C. Marsh, R.K. Simons
Start Date: May 2005 End Date: August 2005

Granting Agency:Canadian Institutes of Health Research
Total amount of grant: $5,000 CAN

Name of Project: Evaluation of Community-Based Transitional Care for Injection Drug Users Requiring Intravenous Antibiotics.
PI: D.C. Marsh Co-Investigators: B. Stein, D. Elliott, E. Drucker, D. Small, B. Stiver, A. Hill, A. Palepu, A.Wei
Start Date: April, 2005 End Date: Dec. 2005
Granting Agency: Vancouver Coastal Health
Total amount of grant: $100,000 CAN

Name of Project: Evaluation of the HyWiRe Project.
PI: A. Anis, D.C. Marsh
Start Date: April, 2005 End Date: June, 2007
Granting Agency: Vancouver Coastal Health
Total amount of grant: $400,000 CAN

Name of Project: Evaluation of the Impact of Welfare Cheque Issue on Utilization of Withdrawal Management.
PI: A. Anis, D.C. Marsh
Start Date: April, 2004 End Date: March, 2005
Granting Agency: Vancouver Coastal Health
Total amount of grant: $25,000 CAN

Name of Project: Smoking Cessation in Addiction and Mental Health Treatment: Professional Roles, Attitudes and Practices.
PI: J. Brewster Co-Investigators: D.C. Marsh, W. Skinner
Start Date: November, 2003 End Date: October, 2004
Granting Agency: Canadian Tobacco Control Research Initiative
Total amount of grant: $29,990 CAN

Name of Project: Methadone Program Recipients and Providers Study.
PI: C. Strike Co-Investigators: D.C. Marsh, B. Fischer, P. Millson
Start Date: April, 2002 End Date: March, 2003
Granting Agency: Research in Psychiatry Grants Program
Total amount of grant: $5,300 CAN

Name of Project: Illicit Opiate Addiction, Treatment and Policy in Canada: A Cross-Disciplinary, Comprehensive and Concerted Research Initiative.
PI: B. Fischer Co-Investigators: D.C. Marsh, S. Brissette, S. Brochu, J. Bruneau, N. el-Guebaly, P. Lauzon, M. O'Shaughnessy, C. Poulin, J. Rehm, M. Schechter, E. Single, J. Stewart, M. Tyndall, C. Wild.
Start Date: July 2001 End Date: December 2005
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $3,469,939 CAN

Name of Project: The Comparative Pharmacological Effects of Temazepam, Diphenhydramine and Valerian in Elderly Subjects.
PI: U. Busto Co-Investigators: B. Sproule, N. Herrmann, D. Streiner
Consultants: D.C. Marsh, P. Selby
Start Date: April, 2001 End Date: April, 2004
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $174,000 CAN

Name of Project: Adolescent Heroin Use-Bridging the Gap to Treatment.
PI: B. Brands Co-Investigators: K. Leslie, L. Catz-Biro, J. Blake, D.C. Marsh
Start Date: April, 2001 End Date: March, 2002
Granting Agency: Research in Psychiatry Grants Program

Total amount of grant: $5,000 CAN

Name of Project: Comparative study of the subjective and physiological effects of heroin and hydromorphone administered intravenously versus subcutaneously.
PI: B. Brands Co-PI: D.C. Marsh Co-Investigators: U. Busto, G. Bigelow
Start Date: October, 1999 End Date: April, 2003
Granting Agency: Open Society Institute
Total amount of grant: $120,000 US

Name of Project: A randomized, double-blind, placebo-controlled, 12-week smoking cessation trial of ZYBAN (150mg bid) in adult smokers previously treated with Zyban.
PI: P. Selby Co-PI: B. Brands Co-Investigators: W. Corrigall, D.C. Marsh
Start Date: November, 1999 End Date: November, 2000
Granting Agency: Glaxo
Total amount of grant: $60,000 CAN

Name of Project: Illicit Opiate Addiction in Canada - Building a Research Agenda for Science, Treatment and Policy.
PI: B. Fischer Co-Investigators: D. Marsh, J. Negrete, M. O'Shaughnessy, J. Stewart
Start Date: October, 1999 End Date: October, 2000
Granting Agency: Canadian Institutes of Health Research
Total amount of grant: $24,000 CAN

Name of Project: Pilot Testing On a Pocketbook on Management of Substance Use Disorders for Physicians and Nurses.
PI: M. Kahan Co-Investigators: D.C. Marsh, L. Wilson
Start Date: September, 1999 End Date: April, 2001
Granting Agency: Lawson Foundation
Total amount of grant: $25,000 CAN

Name of Project: Best Practices in Methadone Maintenance Treatment.
PI: B. Brands Co-PI: D.C. Marsh Co-Investigators: L. Hart, W. Jameson
Start Date: March, 1999 End Date: June, 2001
Granting Agency: Health Canada
Total amount of grant: $42,000 CAN

Name of Project: Pharmacology of the Rat Oesophageal Myenteric Plexus.
PI: D.C. Marsh Supervisor: D. Bieger
Start Date: April, 1986 End Date: January, 1990
Granting Agency: Medical Research Council, Studentship
Total amount of grant: $45,000 CAN

Invited Lectures

The IV International Congress on Dual Disorders (ICDD 2015)
Barcelona, Spain – April 18, 2015
Invited Speaker: *Response to injectable opioid treatment in participants with moderate vs. low psychopathology symptoms*

NRHA Rural Medical Education Conference
Philadelphia, PA – April 14, 2015
Invited Speaker: *Rural focused admissions for a new rural program*

Canadian Recruit and Retain Conference
Thunder Bay, ON, January 15 – 17, 2014
Plenary Speaker: *Community Engaged Medical Education as a Means to Physician Recruitment and Retention.*

Addictions Awareness Conference: Trauma – Helping and Healing
Chatham ON, November 11, 2013
Invited Speaker: Community Engagement and Harm Reduction

Consortium of Universities for Global Health 4th Annual Conference
Global Health: Innovation, Implementation, Impact
March 14 – 16, 2013 Washington DC
Invited panel participant on: *Scaling Up for Impact: Increasing the Impact of Academic Institutions on the Development of Equitable Health Systems*

Ontario Psychiatric Outreach Programs
Sault Ste. Marie, ON September 14, 2012
Invited Speaker on *History of Opioid Agonist Treatment in Canada*

Addictions Symposium
London, ON November 25, 2011
Invited Plenary Speaker on *Addictions: A Global Perspective*

Canadian Society of Addiction Medicine 23rd Annual Scientific Conference
Vancouver, BC November 4 – 6, 2011
Invited Plenary Speaker on *History of Opioid Agonist Treatment in Canada*

Monash University-wide Symposium
Monash University, Melbourne, Australia, July 6, 2011
Invited Speaker on *Social Accountability in Medical Education: Aboriginal Peoples Health and the Northern Ontario School of Medicine*

ANZAHPE 2011 Conference
Alice Springs, Australia June 28 – 30, 2011
Invited Speaker on *Social Accountability through Medical School Admissions*

Northern Health Research Conference
North Bay, ON, June 10-11, 2011
Invited Speaker on *Do Guidelines Influence Physician Behaviour? Case Study of MMT in British Columbia: 1996-2007*

HIV Antiretroviral Update
BC Centre for Excellence in HIV/AIDS
Vancouver, BC, June 11, 2010
Invited speaker on *Addiction and HIV*

International Drug Policy Reform Conference (Drug Policy Alliance Network)
Albuquerque, NM, November 1-14, 2009
Invited panel participant on *Drug Courts: Is a Kinder, Gentler Drug War Good Enough?*
Invited panel participant on *Heroin-Assisted Treatment*

Diversity Matters: An Ongoing Conversation
Vancouver, BC, November 2-3, 2009
Invited workshop presenter on *Best practices in providing ethno-cultural care within mental health and addictions: reviewing the literature and practices of Canadian organizations*.

Pamela Fralick Forum - Addiction by Prescription: Preventing and treating opioid dependence resources
Sudbury, ON, October 13-14, 2009
Invited speaker on *What You Should Know about Prescribed Opioids and Working with Patients who are Addicted*

International Society of Addiction Medicine Annual Conference
Calgary, AB, September 23-25, 2009
Invited Chair for *MMT & HEROIN* session and presenter on *NAOMI report*

Canadian Society of Addiction Medicine Annual Scientific Meeting
Calgary, AB, September 26, 2009
Invited speaker on *Normalization and Stigmatization of Cannabis and Tobacco Use in Young Canadian Adults*

Canadian Society of Addiction Medicine 20th Annual Scientific Meeting
Vancouver, BC, October 30 to November 1, 2008
Invited plenary speaker on *Methamphetamine in British Columbia*.

First Francophone Conference on Treatment of Opioid Dependence
Montreal, QC, October 22 – 24, 2008
Invited plenary speaker on *Heroin-Assisted Treatment*.

First Global Conference on Methamphetamine
Prague, Czech Republic, September 15 – 16, 2008
Invited plenary speaker on *Methamphetamine in British Columbia, Canada*.

American Society of Addiction Medicine, 40th Annual Medical-Scientific Conference
Toronto, ON April 11 – 14, 2008
Invited panel speaker on *Opioid Agonist Treatment.*

2nd International Drug Policy Reform Conference
New Orleans, Louisiana, US, December 6 - 10, 2007
Invited to organize a panel on: *Heroin Assisted Treatment*

Alberta College of Physician Annual Internal Medicine Conference
Banff, AB, November 14 - 17, 2007
Invited plenary speaker on *Identification and Management of Substance Abuse*

Canadian Society of Addiction Medicine 19th Annual Scientific Meeting
Ottawa, ON, October 10 - 13, 2007
Invited plenary speaker on *Opportunities and Barriers to the Role of Physicians in Interdisciplinary Addiction Care.*

Sixth Interdisciplinary Substitution Treatment Symposium
Montreal, QC. November 30 to December 1, 2006
Invited speaker on: *Supervised Injection Facilities*

BC Provincial Court Judges Conference
Vancouver, BC, November 23, 2006
Invited speaker on *Addiction Treatment and the Criminal Justice System*

4th Annual United States Harm Reduction Conference
Oakland, CA, USA, November 9 - 12, 2006
Invited speaker on *The North American Opiate Medication Initiative (NAOMI)*

Heroin Trials Network Meeting,
Amsterdam, October 25, 2006
Invited Participant

Heroin-assisted treatment – an innovative element of the drug support system
Cologne, Germany, March 23-25, 2006
Invited speaker on *The North American Opiate Medication Initiative (NAOMI)*

2005 International Drug Policy Reform Conference
Long Beach, California, UDS, November 10-12, 2005
Invited to organize a panel on: *Harm Reduction* including delivering a talk on the *Canadian Heroin Trial*

Canadian Society of Addiction Medicine 17th Annual Scientific Meeting
Vancouver, BC, October 30, 2005
Invited plenary speaker on *Update on the North American Opiate Medication Initiative.*

Institute of Neurosciences, Mental Health and Addiction 4th Annual Meeting
Vancouver, BC, October 14-15, 2005
Invited panel speaker on *Addictions*

Keeping the Door Open, Lockdown: Drugs, Prisons and Disease in Our Society
Vancouver, BC, June 21, 2005
Invited plenary speaker on *Addiction Treatment and Incarceration.*

Community Mental Health Services, Annual David Berman Conference on Concurrent Disorders
Vancouver, BC, June 1, 2005
Invited speaker on *Psychopharmacology of Substance Use Disorders*

American Society of Addiction Medicine, 37th Annual Medical-Scientific Conference
Dallas, TX, USA, April 14 – 17, 2005
Invited panel speaker on *Office-Based Opioid Agonist Treatment.*

Faculty of Medicine, UBC, Med II Medicine and Society Course
Vancouver, BC, March 16, 2005
Invited lecture on *Harm Reduction*

Nova Scotia Ministry of Health, Think Tank on Methadone Maintenance Treatment
Halifax, NS, March 8 – 9, 2005
Invited plenary speaker on *Evidence-Based Treatment of Opioid Dependence*

Health Canada, Special Seminar
Ottawa, ON, February 28, 2005
Invited speaker on *Update on Supervised Injection Site and North American Opiate Medication Initiative*

Health Care and Epidemiology, UBC, Departmental Rounds
Vancouver, BC, February 18, 2005
Invited lecture on *Supervised Injection Site.*

Memorial University of Newfoundland, Special Seminar for Department of Psychiatry
St. John's, NL, December 22, 2004
Invited lecture on *Treatment of Opioid Dependence.*

Centre for Addiction Research – BC, Continuing Education Series
Victoria, BC, December 9, 2004
Inviter speaker on *North American Opiate Medication Initiative*

Western Canadian Conference on Addiction and Mental Health, 1st Conference
Richmond, BC, November 19 - 20, 2004
Invited speaker on *Harm Reduction*

Department of Medicine, UBC, Seminar for PGYI Residents
Vancouver, BC, October 26, 2004
Invited speaker on *Overview of Addiction Medicine.*

Canadian Society of Addiction Medicine 16th Annual Scientific Meeting
Toronto, ON, October 21 -24, 2004
Invited plenary speaker on *Evaluation of a Supervised Injection Facility.*

American Association for the Treatment of Opioid Dependence, 20th Anniversary Conference
Orlando, FL, USA, October 16 - 20, 2004
Invited speaker on *Opioid Agonist Treatment in Canada.*

Department of Psychiatry, UBC, Seminar for PGYIV and PGYV Residents
Vancouver, BC, October 7, 2004
Invited speaker on *Addiction Treatment in Older Adults.*

Vancouver General Hospital Grand Rounds
Vancouver, BC, September 28, 2004
Invited speaker on *Psychopharmacology of Substance Use Disorders.*

Keeping the Door Open, Moving Forward: Improving Treatment for Heroin Addiction
Vancouver, BC, September 20 – 21, 2004
Invited plenary speaker on *Evidence-Based Opioid Agonist Treatment Options.*

Department of Psychiatry, UBC, 3rd Annual Psychiatry Clinical Day
Vancouver, BC, June 11, 2004
Invited speaker on *Psychopharmacology of Substance Use Disorders.*

Community Mental Health Services, Annual David Berman Conference on Concurrent Disorders
Vancouver, BC, May 26, 2004
Invited speaker on *Psychopharmacology of Substance Use Disorders*

Department of Psychiatry, Providence Health Care, Continuing Medical Education Event
Vancouver, BC, April 15, 2004
Invited speaker on *Concurrent Disorders.*

Faculty of Medicine, UBC, Med II Medicine and Society Course
Vancouver, BC, March 10, 2004
Invited lecture on *Harm Reduction*

Alberta Harm Reduction Coalition, 5th Annual Harm Reduction Conference

Edmonton, AB, March 4-7, 2004
Invited keynote speaker on *Canadian Heroin Prescription Trial.*

Albert Einstein College of Medicine and Montefiore Medical Centre, New York, NY
Visiting Professor, December 1-5, 2003 (including invited lectures at the New York Academy of Medicine and the Drug Policy Foundation)

College of Physicians and Surgeons of Ontario – Methadone Prescribing Physicians Annual CME Day
Toronto, ON, November 17, 2003
Invited keynote speaker on *Methadone Maintenance in Ontario, Recent Evidence for Effectiveness*

Health Canada, National Research Forum on Addiction
Ottawa, ON, October 2-4, 2003
Invited participant on meeting to set research agenda for Canada under new federal drug strategy

National Institute of Drug Abuse, Addiction and Primary Care Meeting
Bethesda, MD, July 17-18, 2003
Invited speaker and panel discussant on *Addiction Medicine and Primary Care in Canada*

New Mexico Department of Health, Behavioral Health Services Division, Southwest Regional Behavioral Health Conference
Albuquerque and Sante Fe, NM, USA, February 13-14, 2003
Invited keynote speaker on *Office-Based Opioid Addiction Treatment.*

Canadian Institute of Underwriters Education Committee Seminar on Substance Use Disorders
Toronto, ON, January 28, 2003
Invited keynote speaker on *Substance Use Disorders.*

San Francisco Department of Public Health Office-Based Opioid Addiction Treatment Project
San Francisco, CA, USA, January 22, 2003
Invited small group facilitator for ASAM course on *Buprenorphine in Office Based Treatment of Opioid Dependence.*

The Royal Society of Canada Symposium "Addictions: Impact on Canada"
Ottawa, ON, November 23, 2002
Invited keynote speaker on *Pharmacotherapy of Substance Use Disorders.*

Canadian Society of Addiction Medicine 13th Annual Scientific Meeting
Banff, AB, October 19, 2001
Invited speaker on *Overview of Addiction for Addiction Fundamentals Course.*

Bridging the Gap: Harm Reduction Policy for Substance Abuse, STD and HIV Resolution Conference
San Francisco, CA, USA, January 11, 2001
Invited speaker on *International Models of Harm Reduction.*

Third National Harm Reduction Conference
Miami, FL, USA, October 24, 2000
Invited to seat on a panel on *Heroin Prescription Trials.*

Berkeley Addiction Treatment Services
San Francisco, CA, USA, September 28 and 29, 2000
Invited to deliver a 2-day training on *Methadone Maintenance Treatment.*

CIHR-Funded Workshop on Illicit Opiate Addiction in Canada
Toronto, ON, June 1-3, 2000

Invited speaker on *Alternative Pharmacotherapies To Methadone Maintenance.*

North Eastern Regional Doctors' Symposium
Baddeck, Nova Scotia, May 20, 2000
Invited keynote speaker on *The Prescription Pad as Your Fiend in Treating Addictions.*

General Practice Psychotherapy Association, Annual General Meeting
Toronto, ON, May 12, 2000
Invited keynote speaker on *Behavior Change and Motivational Enhancement.*

Canadian Society of Addiction Medicine 11th Annual Scientific Meeting
Montreal, PQ, October, 1999
Co-facilitated a pre-conference workshop on *Overview of Addiction Medicine* and
Invited panelist and spoke on *A Canadian Heroin Trial?*

Nova Scotia Provincial Advisory Committee on Methadone
Halifax, NS, October, 1999
Invited speaker on *Methadone Maintenance in Ontario*.

Bridging the Gap: Harm Reduction in Treatment Conference
San Francisco, USA, May, 1999
Invited speaker and co-facilitator for a 3-hour workshop on *Methadone Maintenance and Harm Reduction.*

Bermuda Ministry of Health
Hamilton, Bermuda, April, 1999
Invited to deliver a 2-day training event on *Methadone Maintenance Treatment.*

International Harm Reduction Conference
Geneva, Switzerland, March, 1999
Invited panelist to speak on *A Canadian Heroin Trial?*

San Francisco Office-Based Opiate Agonist Prescribing Project
San Francisco, USA, January, 1999
Invited speaker on *Methadone Maintenance in Ontario.*

New York Academy of Medicine, Conference on Expanded Pharmacological Treatment of Drug Dependence
New York, USA, September, 1998
Invited to chair a panel on *Novel Models of Methadone Maintenance* and speak on *Methadone Maintenance in Ontario.*

New York Academy of Medicine, 1st International Conference on Heroin Maintenance
New York, USA, June, 1998
Invited to chair a panel on C*linical and Treatment Issues* and speak on *A Canadian Perspective.*

Addiction Treatment Services Association, Prescription Drug Abuse Conference
St. John's, NF, May, 1998
Keynote speaker and delivered a 3-hour workshops on *Benzodiazepine Dependence: From Neuroscience to Clinical Applications* and on *Opiate Dependence: Clinical Applications of Harm Reduction and Management of Pain.*

Canadian Society of Addiction Medicine 9th Annual Scientific Meeting
Halifax, NS, October, 1997
Co-facilitated a pre-conference workshop on *Methadone Maintenance Treatment.*

Government Consultations

Invited to witness before the Committee on the topic of *Adult Disorders*.
Standing Senate Committee on Social Affairs, Science and Technology / Senate of Canada
Toronto, ON, May 29, 2003.

Invited Participant, International Experts Forum 2002: Setting the Agenda for Correctional Research in Substance Abuse, Addictions Research Centre, Correctional Service Canada (Charlottetown, PEI,
April 30 - May 2, 2002)

Invited Participant, Municipal Forum on Supervised Injection Sites, Office of Canada's Drug Strategy, Canadian Centre on Substance Abuse, Health Canada (Ottawa, ON, March 25, 2002)

New Mexico Department of Health, Behavioral Health Services Division, Southwest Regional Behavioral Health Conference
Albuquerque, NM, USA, March 13, 2002
Invited keynote speaker on *New Directions in Community Based Addiction Treatment for Opiate Dependency.*

House of Commons, Special Committee on Non-Medical Use of Drugs
Toronto, ON, February 19, 2002
Invited to speak on a panel on *Harm Reduction.*

Alcohol & Drug Services Development, Vancouver/Richmond Health Board
Vancouver, BC, October 22-23, 2001
Invited keynote speaker on *Methadone Maintenance in a Residential Treatment Setting* and *Clinical Heroin Trials.*

Member of Sub-Committee of the Ontario Advisory Committee on HIV/AIDS to advise the Minister of Health on Mandatory Drug Testing for Welfare Recipients (2001-2003)
Health Canada

Ottawa, ON, April 27, 2000
Invited to testify before Health Canada Federal, Provincial, Territorial Working Group on Injection Drug Use on *the North American Opiate Medication Initiative.*

The Vermont State Legislature
Montpelier, Vermont, USA, Feb-April, 2000
Invited expert witness for hearings in both Senate and House of Vermont Legislature concerning *proposed bill to introduce methadone maintenance therapy for opioid dependence.*

Saskatchewan Ministry of Health
Regina, SK, November 26 and 27, 1999
Invited to deliver a 2-day training event on *Methadone Maintenance Treatment.*

Saskatchewan Ministry of Health
Saskatoon, SK, November 24 and 25, 1999
Invited to deliver a 2-day training event on *Methadone Maintenance Treatment.*

Member of External Advisory Committee on Methadone, College of Physicians and Surgeons of Ontario (1997 - 1999)

Academic Service

CIHR Centres for HIV/AIDS Research Committee (2014 – present)

Deputy Editor, Harm Reduction Journal (2008 – present)

Member of the College of Physicians and Surgeons of British Columbia Methadone Committee (2009 - 2010)

Invited Consultant to San Francisco Department of Public Health OBOAT Project (2003 - 2007)

Mentor for Collaborative Mental Health Care Network, Ontario College of Family Physicians
(2001- 2003)

President, Canadian Society of Addiction Medicine (2003 – 2006);
Ontario Board Representative (2000-2003), President-Elect (2002 – 2003)

Member of the College of Physicians and Surgeons of Ontario Methadone Committee (1999 - 2003)

Member Board of Inquiry, College of Physicians and Surgeons of Ontario (1996 – 2003)

Designated Faculty, American Society of Addiction Medicine, Buprenorphine and Office-based Treatment of Opioid Dependence (2002)

President and Chairman of the Board, General Practice Psychotherapy Association (1997 - 1999)

Member Board of Directors, General Practice Psychotherapy Association (1996 - 1997)

Chair Medical Consultant Team, Addiction Clinical Consultation Service a province-wide, toll-free phone support for health care professionals (1995 - 1997)

Chairman of Educational Rounds, Addiction Medicine Clinic, Addiction Research Foundation (1995 -1997)

Academic Journal Contributions

Peer Reviewer for the following: *Addiction; Addiction Theory and Research; Substance Use and Misuse; Harm Reduction Journal; Journal of Substance Use, International Journal of Drug Policy*

Editorial Board: *Harm Reduction Journal*

Professional Memberships

Canadian Society of Addiction Medicine
College of Family Physicians of Canada
General Practice Psychotherapy Association
International Harm Reduction Association
American Society of Addiction Medicine
Ontario College of Family Physicians
Christian Medical Dental Society of Canada
International Society of Addiction Medicine

Papers

Under Review

Corresponding Author: Zainab Samaan. Co-Authors: Monica Bawor, Brittany B Dennis, Charlie Tan, Guillaume Pare, Michael Varenbut, ; Jeff Daiter, Carolyn Plater, Andrew Worster, David C Marsh, Meir Steiner, Rebecca Anglin, Dipika Desai, Lehana Thabane (2015. **Contribution of BDNF and DRD2 genetic polymorphisms to continued opioid use in patients on methadone treatment for opioid use disorder** (submitted to Comprehensive Psychiatry)

Dennis, B.B., Roshanov, P., Naji, L. Bawor, M., Varenbut, M., Daiter, J., Plater, C., Pare, G., Marsh, D.C., Worster, A., Desai, D.,

Thabane, L., Samaan, Z. (2015). **Comparative Effectiveness of Opioid Maintenance Treatments for Patients with Opioid Addiction: A Multiple Treatments Comparison and Network Meta-analysis.** (In review with Lancet)

Naji, L., Dennis, B., Bawor, M., Paul, J., Plater, C., Pare, G. Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Thabane, L., Samaan, Z. (2015) **Pathways to Concurrent Illness: Age of Onset of Opioid Abuse as a Predicator of Physical Comorbidity Among Opioid Dependent patients.** (In review with Journal of Addiction)

Dennis, BB., Bawor, M., Paul, J., Plater, C., Pare, G. Worster, A., Varenbut, M., Daiter, J., Marsh, DC., Desai, D., Thabane, L., Samaan, Z. (2015) **The GENOA Risk Evaluation Tool (GREAT) for Treatment Response in Methadone Maintenance Treatment.** (In review with Substance Abuse and Rehabilitation).

Dennis, B., Roshanov, P., Naji, L., Bawor, M., Paul, J., Plater, C., Pare, G. Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Thabane, L., Samaan, Z. (2015) **The Real Opioid Addiction Patients: Left Out of Trials and Ignored by Guidelines.** (In review with Addiction in January 2015)

Dennis, B., Bawor, M., Plater, C., Pare, G. Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Thabane, L., Samaan, Z. (2014) **Pain and Opioid Addictions: a systematic review and validation of pain measurement in patients with opioid dependence** (In review with Behavioural Neurology in January 2015)

Dennis, B.B., Bhalareo, A., Plater, Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Steiner, M., Anglin, R., Pare, G., Thabane, L., Samaan, Z. (2015). **Men and women respond differently to methadone treatment for opioid addiction: A systematic review and meta-analysis.** (In review with CMAJ Open, Sept. 2014).

Published

Dennis, B.B., Bawor, M., Paul, J., Plater, C., Pare, G., Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Thabane, L., and Samaan, Z. (2015). **The Impact of Chronic Pain on Opioid Addiction Treatment: A systematic Review Protocol.** Systematic Reviews (2015) 4:49

Oviedo-Joekes E, Sordo L, Guh D, Marsh DC, Lock K, Brissette S, Anis AH, Schechter MT. **Predictors of non-use of illicit heroin in opioid injection maintenance treatment of long-term heroin dependence.** Addict Behav. 2015 Feb;41:81-6.

Monica Bawor, Herman Bami, Brittany B. Dennis, Carolyn Plater, Andrew Worster, Michael Varenbut, Jeff Daiter, David C. Marsh, Meir Steiner, Rebecca Anglin, Margaret Coote, Guillaume Pare, Lehana Thabane, Zainab Samaan. **Testosterone suppression in opioid users: A systematic review and meta-analysis.** Drug and Alcohol Dependence (2015) 1-9.

Siavash Jafari, Ronald Joe, Danielle Elliot, Ashnoor Nagji, Sargent Haydent, David C. Marsh. **A Community Care Model of Intravenous Antibiotic Therapy for Injection Drug users with Deep Tissue Infection for "Reduce Leaving against Medical Advice"** International Journal of Mental Health and Addiction. (2015) 13:40-58

Dennis BB, Samaan CM, Bawor M, Paul J, Plater C, Pare G, Worster A, Varenbut M, Daiter J, Marsh DC, Desai D, Thabane L, Samaan Z. **Evaluation of clinical and inflammatory profile in opioid addiction patients with comorbid pain: results from a multicenter investigation.** Neuropsychiatric Disease and Treatment: 2014 Nov 19; 10:2239-47.

Oviedo-Joekes E, Marchand K, Lock K, Chettiar J, Marsh DC, Brissette S, Anis AH, Schechter MT. **A chance to stop and breathe: participants' experiences in the North American opiate medication Initiative *clinical trial.*** Addiction Science & clinical Practice 2014 Sep 29; 9:21

Bawor, M., Dennis, BB., Samaan, M.C., Plater, C., Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Steiner, M., Anglin, R., Coote, M., Bami, H., Pare, G., Thabane, L., Samaan, Z., (2014) **Testosterone suppression and methadone treatment in men and women: A cross-sectional study of patients treated for opioid dependence with methadone.** (Accepted with Scientific Reports, August 2014)

Asbridge M, Duff C, Marsh DC, Erickson PG. **Problems with the Identification of "Problematic" Cannabis Use: Examining the Issues of Frequency, Quantity, and Drug Use Environment**. Eur Addict Res 2014; 20:254-267.

Oviedo-Joekes E, Guh D, Marchand K, Marsh D, Lock K, Brissette S, Anis AH, Schechter MT.: **Differential long-term outcomes for voluntary and involuntary transition from injection to oral opioid maintenance treatment**. Substance Abuse Treatment, Prevention, and Policy 2014, 9:23.

Dennis BB, Naji L, Bawor M, Bonner A, Varenbut M, Daiter J, Plater C, Pare G, Marsh DC, Worster A, Desai D, Samaan Z, Thabane L.; **The Effectiveness of Opioid Substitution Treatments for Patients with Opioid Dependence: A Systematic Review and Multiple Treatment Comparison Protocol.** Systematic review 2014 Sep 19; 3:105

Oviedo-Joekes E, Guh D, Marchand K, Marsh DC, Lock K, Brissette S, Anis AH, Schechter MT. **Differential long-term outcomes for voluntary and involuntary transition from injection to oral opioid maintenance treatment.** Subst Abuse Treat Prev Policy. 2014 Jun 8;9:23.

Mistry CJ, Bawor M, Desai D, Marsh DC, Samaan Z.; **Genetics of Opioid Dependence: A Review of the Genetic Contribution to Opioid Dependence**. Current Psychiatry Reviews, 2014 May; 10(2):156-167.

Oviedo-Joekes E, Sordo L, Guh D, Marsh D, Lock K, Brissette S, Anis AH, Schechter MT.; **Achieving Non-use of Illicit Heroin in the Context of Medically-prescribed Injectable Diacetylmorphine**. Submitted, PLOS ONE.

Samaan Z, Thabane L, Desai D, Marsh D, Daiter, J, Varenbut M, Worster A, Pare G, Plater C, Paul J, Bawor M, Constantine M, Dennis B.; **Chronic Pain Impacts Response to Methadone Treatment: A Clinical Investigation of Continued Opioid Abuse and Inflammatory Cytokines in Opioid Use Disorder**. (Submitted to Journal of Clinical Psychiatry, May 2014).

Samaan Z, Bawor M, Dennis BB, Plater C, Worster A, Varenbut M, Daiter J, Marsh DC, Desai D, Thabane L, Pare G. **"Genetic influence in methadone dose and response to treatment in patients undergoing Methadone Maintenance Treatment (MMT) for opioid addiction: A pilot study".** Neuropsychiatric Disease and Treatment, May 2014:10.

Nosyk B.; Fischer B.; Sun H.; Marsh DC.; Kerr T.; Rehm J.; Anis AH**.; High Levels of Opioid Analgesic Co-prescription among Methadone Maintenance Treatment Clients in British Columbia, Canada: Results From a Population-level Retrospective Cohort Study.** The American Journal on Addictions, 2014 May; 23(3):257-64.

Bawor M, Dennis BB, Samaan MC, Plater C, Worster A, Varenbut M, Daiter J, Marsh DC, Desai D, Steiner M, Anglin R, Coote M, Pare G, Thabane L, Samaan Z. **"Methadone induces testosterone suppression in patients with opioid addiction"**. Scientific Reports, 2014(4).

MacPhee M, Paterson M, Tassone M, Marsh D, Berry S, Bainbridge L, Steinberg M, Careau E and Verma S; **Transforming health systems through collaborative leadership: Making change happen!** Service –Learning across the globe: from local to transnational Paper Series. 2013(10) 79-82.

Li X, Sun H, Marsh DC, Anis AH. **Factors associated with pretreatment and treatment dropouts: comparisons between Aboriginal and non-Aboriginal clients admitted to medical withdrawal management.** Harm Reduction Journal 2013 Dec 10; 10:38.

Nosyk B.; Anglin MD.; Brissette S.; Kerr T.; Marsh DC.; Newman RG.; Schackman BR.; Wood E.; Montaner JSG. **A call for evidence-based medical treatment of opioid dependence in Canada and the United States**. Health Aff (Millwood). 2013 Aug; 32(8):1462-9

Sharif B, Nosyk B, Sun H, Marsh DC, Anis A. **Changes in the characteristics and levels of comorbidity among new patients into methadone maintenance treatment program in British Columbia during its expansion period from 1998-2006.** Substance Use Misuse. 2013 Jun;48(8):671-82

Strasser R.; Hogenbirk J.C.; Minore B.; Marsh D.C.; Berry S.; McCready W.G.; Graves L. **Transforming Health Professional Education Through Social Accountability: Canada's Northern Ontario School of Medicine.** Med Teach. 2013 Jun; 35(6):490-6. Doi: 10.3109/0142159X.2013.774334. Epub 2013 Mar 15. PMID: 23496120 [PubMed - indexed for MEDLINE]

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Nosyk B, Guh DP, Bansback NJ, Oviedo-Joekes E, Brissette S, Marsh DC, Meikleham E, Schechter MT, Anis AH. **Cost-Effectiveness of Diacetylmorphine versus Methadone for Chronic Opioid Dependence Refractory to Treatment.** CMAJ. 2012 Apr 3; 184(6):E317-28

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Nosyk B; Sun H; Evans E; Marsh DC; Anglin MD; Hserr YI; Anis AH. **Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: Results from a population-based retrospective cohort study.** Addiction 2012 Sep; 107(9):1621-9.

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Marchand, K.; Oviedo-Joekes, E.; Guh, D.; Marsh, D.; Brissette S. and M.T. Schechter**. Sex work involvement among women with long-term opioid injection drug dependence who enter opioid agonist treatment**. Harm Reduction Journal 2012 9:8

Duff, Cameron; Asbridge, Mark; Brochu, Serge; Cousineau, Marie-Marthe; Hathaway, Andrew D; Marsh, David; Erickson, Patricia G. **A Canadian Perspective on Cannabis Normalization among Adults**. Addiction Research & Theory. 2012 20(4):271-283.

Marchand K; Oviedo-Joekes, E.; Guh, D.; Brissette, S.; Marsh, D. and M.T. Schechter. **Client satisfaction among participants in a randomized trial comparing oral methadone and injectable diacetylmorphine for long-term opioid-dependency**. BMC Health Services Research 2011; 11:174-183

DeBeck K, Kerr T, Bird L, Zhang R, Marsh D, Tyndall M, Montaner J, Wood E. **Injection Drug Use Cessation and Use of North America's First Medically Supervised Safer Injecting Facility.** Drug Alcohol Depend. 2011 Jan 15; 113(2-3):172-6

Nosyk, B., Guh, D., Sun, H., Oviedo-Joekes, E., Brissette S., Marsh, D.C., Schechter M.T., Anis, A.H., **Health related quality of life trajectories of patients in opioid substitution treatment.** Drug and Alcohol Dependence 2011:118(2-3):259-264

Oviedo-Joekes E, Guh D, Brissette S, Marchand K, Marsh DC, Krausz M, Anis A, Schechter MT. **History of reported sexual or physical abuse among long-term heroin users and their response to substitution treatment.** Addictive Behaviors 2011; 36 (1-2):55-60.

Oviedo-Joekes E, Guh D, Marsh DC, Brissette S, Nosyk B, Krausz M, Anis A, Christian WM, Spittal P, Schechter MT. **Characteristics and response to treatment among Aboriginal people receiving heroin-assisted treatment.** Can J Public Health. 2010; 101(3):210-1.

Oviedo-Joekes Eugenia, Guh Daphne, Brissette Suzanne, Marchand Kirsten, Marsh David, Chettiar Jill, Nosyk Bohdan, Krausz Michael, Anis Aslam, and Schechter Martin T. **Effectiveness of diacetylmorphine versus methadone for the treatment of opioid dependence in women.** Drug Alcohol Depend. 2010:111(1-2):50-7

Nosyk B, Geller J, Guh DP, Oviedo-Joekes E, Brissette S, Marsh DC, Schechter MT, Anis AH. **The effect of motivational status on treatment outcome in the North American Opiate Medication Initiative (NAOMI) study.** Drug Alcohol Depend. 2010; 111 (1-2):161-5.

Nosyk, Bohdan; Marsh, David; Sun, Huiying; Schechter, Martin; Anis, Aslam. **Trends in methadone maintenance treatment participation, retention and compliance to dosing guidelines in British Columbia, Canada: 1996-2006**. Journal of Substance Abuse Treatment (2010) 39 (1):22-31.

Nosyk, B; Anis, Guh, D; Sun, H; Oviedo-Joekes, E; Brissette, S; Marsh, D; Schechter, M. **The quality of eight health status measures were compared for chronic opioid dependence.** Journal of Clinical Epidemiology (2010) 63(10):1132-1144.

Oviedo-Joekes, Eugenia; Schechter, Martin; Marsh, David; Brissette, Suzanne; Guh, Daphne; Nosyk, Bohdan; Anis, Aslam; Krausz, Michael.. **Double-blind Injectable Hydromorphone vs. Diacetylmorphine for the treatment of opioid dependence: A pilot study.** Journal of Substance Abuse Treatment 38(4):408-11 (2010).

Hathaway, Andrew; Hyshka, Elaine; Erickson, Patricia G; Asbridge, Mark; Brochu, Serge; Cousineau, Marie-Marthe; Duff, Cameron; Marsh, David. **Whither RDS? An investigation of Respondent Driven Sampling as a method of recruiting mainstream marijuana users**. Harm Reduction Journal 7:15-26 (2010).

Oviedo-Joekes, Eugenia; Schechter, Martin; Marsh, David; Brissette, Suzanne; Guh, Daphne; Nosyk, Bohdan; Spittal, Patricia; Anis, Aslam; Christian, Wayne; Krausz, Michael. **Characteristics and response to treatment among Aboriginal people in North America's first trial on heroin-assisted treatment**. Canadian Journal of Public Health 101:210-212 (2010).

Uhlmann, Sasha; Milloy, M-J; Kerr, Thomas; Zhang, Ruth; Marsh, David; Hogg, Robert; Montaner, Julio; Wood, Evan. **Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users**. Addiction 105(5):907-913 (2010).

Stockwell, Tim; Buxton, Jane; Duff, Cameron; Marsh, David; MacDonald, Scott; Michelow, Warren; Saewyc,Elizabeth; Richard, Krista; Hanson, Robert; Cohen, Irwin; Corrado, Ray; Chow, Clifton, Ivsins, Andrew; Nicholson, Dean; Pakula, Basia; Puri, Ajay; Rehm, Jurgen; Sturge, Jodi; Tu, Andrew; Zhao, Jinhui. **The British Columbia Alcohol and Other Drug Monitoring System: Overview and Early Progress.** Contemporary Drug Problems 36(3&4):459-484 (2009).

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The North American Opiate Medication Initiative (NAOMI): Profile of Participants in North America's First Trial of Heroin-Assisted Treatment

This is Exhibit B referred to in the affidavit of Dr. David Marsh sworn before me, this 25th day of May 20 15
A COMMISSIONER FOR TAKING AFFIDAVITS

Eugenia Oviedo-Joekes, Bohdan Nosyk, Suzanne Brissette, Jill Chettiar, Pascal Schneeberger, David C. Marsh, Michael Krausz, Aslam Anis, and Martin T. Schechter

ABSTRACT *The North American Opiate Medication Initiative (NAOMI) is a randomized controlled trial evaluating the feasibility and effectiveness of heroin-assisted treatment (HAT) in the Canadian context. Our objective is to analyze the profile of the NAOMI participant cohort in the context of illicit opioid use in Canada and to evaluate its comparability with patient profiles of European HAT studies. Recruitment began in February 2005 and ended in March 2007. Inclusion criteria included opioid dependence, 5 or more years of opioid use, regular opioid injection, and at least two previous opiate addiction treatment attempts. Standardized assessment instruments such as the European Addiction Severity Index and the Maudsley Addiction Profile were employed. A total of 251 individuals were randomized from Vancouver, BC (192, 76.5%), and Montreal, Quebec (59, 23.5%); 38.5% were female, the mean age was 39.7 years (SD:8.6), and participants had injected drugs for 16.5 years (SD:9.9), on average. In the prior month, heroin was used a mean of 26.5 days (SD:7.4) and cocaine 16 days (SD;12.6). Vancouver had significantly more patients residing in unstable housing (88.5 vs. 22%; $p<0.001$) and higher use of smoked crack cocaine (16.9 days vs. 2.3 days in the prior month; $p<0.001$), while a significantly higher proportion of Montreal participants reported needle sharing in the prior 6 months (25% vs. 3.7%; $p<0.001$). In many respects, the patient cohort was similar to the European trials; however, NAOMI had a higher proportion of female participants and participants residing in unstable housing. This study suggests that the NAOMI study successfully recruited participants with a profile indicated for HAT. It also raises concern about the high levels of crack cocaine use and social marginalization.*

KEYWORDS *Heroin dependence, Injection Drug Use, Substitution treatment, Cocaine abuse, Treatment refusals*

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INTRODUCTION

Heroin addiction is a chronic relapsing disease and is often accompanied by abuse of other psychoactive drugs, physical and mental health problems, and severe social marginalization.[1,2] The evolution of this disease depends on a genetic contribution, influenced by personal choices and environmental factors, and it can be fatal if not treated.[3] Heroin dependence remains a critical public health problem in Canada and most other parts of the world. Between 75,000 and 125,000 people inject drugs in Canada, with cocaine and heroin the favored injectable substances of choice.[4,5] Institutional sources estimate approximately 80,000 regular opioid users in Canada[6] with geographic differences in prevalence and trends. Although the "street" availability of prescription analgesic opioids such as hydromorphone and morphine has increased in recent years,[7,8] intravenous use of heroin prevails in Vancouver and Montreal.[5,9–11]

Injectors are exposed to life-threatening health risks such as drug overdoses, blood-borne viral infections, endocarditis, and others.[12–14] Those who remain untreated or who are outside the social and health care system are known to experience higher rates of morbidity and mortality.[15–17] Given that abstinence-oriented therapies for opioid addiction have relatively low efficacy,[18] opioid agonist substitution is currently the most effective treatment option.[2] Oral methadone maintenance treatment (MMT) is the most common and accepted formulation and route of administration for substitution treatment. Evidence shows that MMT is effective[19] if delivered under best practices guidelines.[1,20,21]

Although MMT has been proven to be effective for some, it is well documented that a significant proportion of patients are not attracted into or do not respond to this therapy.[22,23] Many nonresponders relapse into the use of illicit street drugs and/or continue injecting illicit opiates even during methadone treatment.[24] For example, in British Columbia, only 52% of MMT patients are retained for at least a year[25] in line with estimates of retention found in the National Institute of Drug Abuse review,[26] but significantly lower than those observed in Ontario,[27] in a low-threshold program in Montreal,[28] and in most of the European countries.[29,30] For nonresponders, there are few alternatives currently available. Heroin-assisted treatment (HAT), in which patients are prescribed pharmaceutical quality heroin (diacetylmorphine) in specialized clinics, is one available therapeutic option for chronic, long-term, opioid injectors who remain outside of the current addiction treatment system. Clinical trials and follow-up studies have demonstrated that prescribed heroin is safe, feasible, and effective.[31–37]

In 2005, a randomized controlled trial with injectable heroin [denoted the North American Opiate Medication Initiative (NAOMI)] began in two Canadian cities (Vancouver and Montreal), aimed at evaluating the feasibility and effectiveness of HAT in the Canadian context. The objective of the present analysis is to describe the profile of the subjects recruited into NAOMI and to evaluate the comparability with international patient profiles of other studies of HAT.

METHODOLOGY

The NAOMI study was designed as an open, randomized controlled trial that compares injected diacetylmorphine (DAM; plus oral methadone if deemed appropriated) with oral methadone alone in the treatment of opioid addiction for chronic injection opioid users who have not benefited from available therapies. Patients in both arms of the trial also receive an identical comprehensive range of psychosocial and primary care

services. The study is being carried out in two sites: the Downtown East Side (DTES) of Vancouver and Montreal.

The original sample size for the trial was 470 based on power calculations to detect absolute differences of 15% between groups in retention and response rates. As the trial progressed, this was relaxed to 20% as recommended by the Drug and Safety Monitoring Board leading to a revised sample size of 253. Recruitment began in February 2005 and ended in March 2007, with 251 participants recruited. The trial was originally planned for three sites, but construction delays and other factors precluded the proposed Toronto site from participating.

The recruitment strategy included an intensive outreach campaign, posters, on-the-street contact, media advertisement, and referrals from services that work with the same target population (e.g., the Vancouver supervised injection facility, needle exchange programs, primary care clinics). The main inclusion criteria included opioid dependence (DSM-IV), minimum of 25 years of age, 5 years or more of opioid use, regular opioid injection, and a minimum of 1 year residence in site/city location. Participants must have had a minimum of two previous opiate addiction treatments, including one in which they received a minimum of 60 mg or more of methadone daily for at least 30 days in a 40-day period. To participate in the study, the candidates could not have been enrolled in methadone maintenance treatment within the prior 6 months. Other exclusion criteria included severe medical or psychiatric conditions that are contraindicated for HAT, pregnancy, and current justice system involvement that could have resulted in an extended period of incarceration during the study period.

The screening period for each participant involved a minimum of 3 weeks from initial contact up to the time when all necessary eligibility criteria had been determined and confirmed (average 6 weeks). As eligible patients completed the screening, they provided informed consent and underwent the baseline assessment. Internationally established standardized assessment instruments were used including the European Addiction Severity Index (EuropASI),[38] SF-6D,[39] EQ5D,[40] WHO-DAS II,[41] and the Maudsley Addiction Profile.[42] Medical examinations and urine-toxicology were performed, and sociodemographic data and relevant institutional data on involvement with drug treatment, health care, and criminal justice were obtained. Following the baseline assessment, participants were randomly allocated to injection-assisted treatment (55%) or methadone maintenance alone (45%). For purposes of validation, a subset of participants in the injection arm was randomly assigned to receive hydromorphone (HDM) instead of DAM on a double-blind basis.

Descriptive analyses were performed for frequencies and means values. Comparisons were carried out using Student's *t*, Mann–Whitney *U*, and Kruskal–Wallis tests for comparisons of means and Chi Square tests for comparisons of frequencies, depending on variable distribution. For comparisons with the European HAT, the following baseline data was used: for The Netherlands, figures from the injection trial ($n=174$)[43]; for Switzerland, patients admitted for a cohort study ($n=1{,}035$)[44]; for Spain, the total sample ($n=62$),[36,45] and for Germany, the "not reached" group ($n=540$).[46] The German trial expressly distinguished between participants from MMT and those not in treatment. Given that the NAOMI study only engaged participants not in MMT, the comparisons were made with the "not reached" strata instead of the whole German sample. Statistical analyses were conducted using SPSS 15.[47]

RESULTS

A total of 1,588 people were contacted and went through the self-report step of the screening process (1,053 in Vancouver and 538 in Montreal), and 581 were assessed for eligibility. Among them, 101 dropped out from the screening process, and 229 were not eligible mainly due to not meeting the MMT history inclusion criteria (they did not get at least 30 days of MMT at 60 mg, or they were currently or recently on MMT, or they did not have a verifiable history of MMT). A total of 251 clients met the eligibility criteria and provided informed consent including 59 (23.5%) in Montreal and 192 (76.5%) in Vancouver (Table 1). Random assignments were as follows: oral methadone 111 (44.2%), injected diacetylmorphine 115 (45.8%), and injected hydromorphone 25 (10.0%).

Sociodemographics

The mean age of the study sample at recruitment was 39.7 years, 38.8% of the participants were female, and 23.9% defined themselves as aboriginal. A total of 72.9% declared that they were living in an unstable housing situation, and 49.8% had been living in their present address for less than 4 months. Montreal participants were younger ($F=18.3$; $p=0.001$), none identified themselves as aboriginal ($\chi^2=24.2$; $p=0.001$), and a much smaller proportion resided in unstable housing ($\chi^2=106.6$; $p=0.001$). The Vancouver site recruited a higher proportion of people living alone while Montreal had a higher number of participants living with people with alcohol problems or who use drugs ($\chi^2=36.18$; $p=0.001$).

Education and Employment

In the prior 3 years, most of the participants had been regularly unemployed (70.9%), and at baseline assessment, only 13.6% had received money from (legal) employment in the prior month. Montreal participants had, on average, more years of education ($t=14.1$; $p=0.001$) than the Vancouver participants, while the reported longest period of unemployment was notably higher among Vancouver participants, even after adjusting for age ($F=18.8$; $p=.001$). Overall, the two most frequently cited sources of income were public assistance (76.1%) and illegal activity (67.3%).

Criminal Activity

Almost all of the participants (94.4%) had been charged at least once in their life for crimes of any nature, 81.7% had been convicted at some point, and the cohort had spent a median of 12 (interquartile 1 and 3 (Q1–Q3)=1–60) months in jail in their lifetime. In the month prior to baseline assessment, 73.3% of the participants were involved in illegal activities (for profit), and the median number of days of illegal activities in the prior 30 days was 15 days (Q1–Q3=0–30). A larger proportion of Vancouver participants had been criminally charged in their lifetime compared to the Montreal participants ($\chi^2=18.9$; $p=0.001$). This difference is significant even after adjusting for age, housing, and crack use in the prior month. There are no differences in relation to the percentage of participants who reported illegal activities during the prior month; however, Vancouver participants reported significantly more days of illegal activity (Mann–Whitney $U=4094.5$; $p=0.001$).

Drug Use

NAOMI participants reported an extensive history of regular drug use, with heroin and cocaine being the most commonly used drugs. Data on recent drug use in the prior

TABLE 1 Patient's eligibility criteria in Montreal and Vancouver

Sociodemographic characteristics	Vancouver ($n=192$) % (n)/M [SD]	Montreal ($n=59$) % (n)/M [SD]	Total ($n=251$) % (n)/M [SD]
Group			
Oral	44.3% (85)	44.1% (26)	44.2% (111)
Injection	55.7% (107)	55.9% (33)	55.8% (140)
Age***	40.9 [8.2]	35.6 [8.6]	39.7 [8.6]
Gender			
Male	61.5% (118)	61.0% (36)	61.4% (154)
Female	38.5% (74)	39.0% (23)	38.6% (97)
First Nation***	31.3% (60)	–	23.9% (60)
Current housing***[a]			
Stable housing	11.5% (22)	78.0% (46)	27.1% (68)
Precarious housing	88.5% (170)	22.0% (13)	72.9% (183)
Living in the current address less that 4 months	49.5% (95)	50.8% (30)	49.8% (125)
Spend free time with family/friends			
Without alcohol or drug problems	9.4% (18)	15.3% (9)	10.8% (27)
With alcohol or drug problems	36.6% (70)	44.1% (26)	38.4% (96)
Alone	53.9% (103)	40.7% (24)	50.8% (127)
Living with anyone with alcohol problems or using drugs***			
No	30.7% (59)	28.8% (17)	30.3% (76)
Yes	16.1% (31)	52.5% (31)	24.7% (62)
Alone	53.1% (102)	18.6% (11)	45.0% (113)
Years of school education***	10.6 [2.1]	11.9 [3.1]	10.9 [2.4]
Generally unemployed[b] in the past 3 years	74.0% (142)	61.0% (36)	70.9% (178)
Longest period of unemployment (months)***	113.5 [83.6]	55.2 [51.0]	99.8 [81.0]
Received money in the prior 30 days for			
Employment	12.5% (24)	17.0% (10)	13.6% (34)
Alternatives sources[c]	32.8% (63)	25.4% (15)	31.1% (78)
Public assistance or welfare*	79.2% (152)	66.1% (39)	76.1% (191)
Mates, family, Or friends**	25.0% (48)	42.4% (25)	29.1% (73)
Illegal sources[§]	70.3% (135)	57.6% (34)	67.3% (169)
Sex work	18.8% (36)	13.6% (8)	17.5% (44)
Charges in life for any crime***	97.9% (188)	83.1% (49)	94.4% (237)
Ever convicted in life***	87.5% (168)	62.7% (37)	81.7% (205)
Months incarcerated in life***[d]	18 (1–72)	3 (0–24)	12 (1–60)
Illegal activities in the prior 30 days	146 (76)	38 (64.4)	184 (73.3)
Illegal activities, days in the prior 30***[d]	20 (1–30)	5 (0–16)	15 (0–30)
Money spent on drugs, prior month[d]	$1,500 [900–3,000]	$1,200 [600–3,000]	$1,500 [900–3,000]

*$p<0.05$; **$p<0.01$; ***$p<0.001$; [§] $p<0.09$

[a]Based on type of housing, not time. Unstable housing was described as having no fixed address, living in a shelter, or living in a SRO (single room occupancy) hotel.

[b]Unemployment includes housewife

[c]Binning, panhandling, shoe-shining, etc.

[d]Median and interquartile ranges

30 days showed similar patterns (Table 2). Cocaine was almost always smoked as crack cocaine a mean days of 13.4 (SD:13.1), and injected as cocaine powder a mean of 5.1 (SD:8.9) days in the prior month. Speedball, a combination of heroin and cocaine, was used a mean of 2.7 (SD:6.4) days the prior month. Besides heroin, nonprescribed methadone, hydromorphone, and morphine were the three most common illicit opioids used by the participants; however, their use was minimal in comparison to heroin use. Compared to Vancouver, Montreal participants reported a higher mean days of use in the prior month of alcohol, injected cocaine, and cannabis. Vancouver participants, however, reported greater use of smoked crack cocaine, amphetamines, speedball, illicit hydromorphone, and illicit morphine.

Health Status and Previous Treatments

Half of the sample (Table 3) reported a significant chronic medical problem, and almost all had been hospitalized at least once (90.8%) in their lifetime. Vancouver participants had higher proportions of chronic health problems and hospitalizations even after adjusting for age and gender. One third of the sample (31.3%) had attempted suicide at least once in their life. In the prior month before randomization, 55% had reported psychological problems, though only 38.2% received psychological treatment in their life, with a higher proportion in Montreal receiving treatment (this difference remained significant after adjusting for age and gender).

Participants had a median of 7 (Q1–Q3=4–14) previous drug treatment attempts including three (Q1–Q3=2–3) methadone treatment episodes. The Montreal participants reported more previous MMT attempts than Vancouver participants (Median=3; Q1–Q3=2–5 vs. Median=3; Q1–Q3=2–3 (2–3); Mann–Whitney $U=4725.5$; $p=0.045$). Almost half of the sample has never remained abstinent for more than 3 months after drug treatment with similar patterns at both sites. Despite shorter lifetime durations of heroin use, Montreal participants reported higher lifetime numbers of overdoses.

TABLE 2 Data on recent drug use in the prior 30 days

	Vancouver ($n=192$)		Montreal ($n=59$)		Total ($n=251$)	
Days of use in the prior month	Mean	SD	Mean	SD	Mean	SD
Alcohol**	2.59	6.50	6.15	9.21	3.43	7.37
Heroin[a,***]	26.82	7.09	25.44	8.39	26.49	7.43
Illicit methadone[b]	1.89	4.47	1.93	4.95	1.90	4.57
Illicit benzodiazepines[b]	2.02	5.98	1.14	4.19	1.81	5.61
Cocaine powder[a]	5.09	9.02	4.90	8.75	5.05	8.94
Crack cocaine[c,***]	16.88	12.69	2.25	6.35	13.41	13.07
Amphetamine[d,*]	1.69	5.39	0.17	0.62	1.33	4.76
Cannabis[c]	6.14	10.51	7.78	11.29	6.53	10.70
Speedball[a]	3.19	6.87	1.12	4.48	2.70	6.44
Illegal hydromorphone[a,§]	2.14	5.71	0.76	4.13	1.82	5.40
Illegal morphine[a,***]	3.92	8.12	0.00	0.00	2.99	7.29
Injecting drugs***	29.06	3.43	24.47	8.26	27.98	5.35
Times injecting drugs in a day**	5.09	3.23	3.61	2.73	4.75	3.18

*$p<0.05$; **$p<0.01$; ***$p<0.001$; §$p<0.09$

[a]More than 95% injected

[b]More than 95% oral

[c]More than 95% smoked

[d]More than 75% injected

TABLE 3 Health status and previous treatments

	Vancouver ($n=192$)		Montreal ($n=59$)		Total ($n=251$)	
Health related events and behaviors	%/*M*	(*n*) [SD]	%/*M*	(*n*) [SD]	%/*M*	(*n*) [SD]
Chronic medical problem[a,**]	58.8%	(113)	35.6%	(21)	53.4%	(134)
Hospitalized in life at least once*	93.2%	(179)	83.1%	(49)	90.8%	(228)
Hepatitis C positive[b]	66.1%	(127)	52.5%	(31)	62.9%	(158)
HIV positive[b]	9.9%	(19)	8.55%	(5)	9.6%	(24)
Ever attempted suicide§	28.4%	(54)	40.7%	(24)	31.3%	(78)
Ever treated for psychological problem*	34.4%	(66)	50.8%	(30)	38.2%	(96)
Psychological problems prior month[§]	48.1%	(91)	62.7%	(37)	55.4%	(128)
Ever alcohol treatment**	28.1%	(54)	8.5%	(5)	22.5%	(59)
Methadone treatment*[,c]	3	2–3	3	2–5	3	2–3
Total number of previous drug treatments[c]	7	4–14	7	4–15	7	4–14
Abstinent after drug treatment						
Never	24.6%	(47)	25.4%	(15)	24.8%	(62)
Less than 3 months	24.6%	(47)	23.7%	(14)	24.4%	(61)
Four months or longer	50.8%	(97)	50.9%	(30)	50.8%	(127)
Years injecting drugs**	17.4	[10.15]	13.4	[8.11]	16.5	[9.85]
Overdoses in life*	3.5	[6.34]	5.9	[10.61]	4.08	[7.60]
Sharing needles in the past 6 months***						
Not sharing needles	96.4%	(185)	74.6%	(44)	91.2%	(229)
Sometimes sharing needles	3.7%	(7)	13.6%	(8)	6.0%	(15)
Often sharing needles	–	(0)	11.9%	(7)	2.8%	(7)
Sharing needles at least once, prior month***	2.1%	(4)	19.0%	(11)	6.0%	(15)
Had sex with *no* condom prior 30 days	19.5%	(37)	28.8%	(17)	21.7%	(54)

*$p<0.05$; **$p<0.01$; ***$p<0.001$; §$p<0.09$
[a]Defined as interfering with life
[b]Self-reported
Missing values: abstinence after drug treatment, 1
[c]Median and interquartile ranges

There were marked differences in risk behaviors between the two cities. A quarter of Montreal participants reported sharing needles sometimes or often in the prior 6 months compared to only 3.7% in Vancouver. Similarly, 19% of Montreal participants reported sharing at least once in the prior month compared to only 2.1% in Vancouver. This difference remained significant even after adjusting for age and use of injected cocaine.

International Comparison

Comparisons with other HAT trial participants' baseline characteristics revealed some similarities and differences with the Canadian sample. The NAOMI participants were somewhat older, but this is not surprising given the inclusion criterion of age 25 or greater. NAOMI participants included more women than any of the European studies. Also, the Canadian sample has a remarkably higher proportion of unstable housing.

Although NAOMI is similar to the other studies with respect to unemployment and frequency of illegal activity, more NAOMI subjects rely on illegal income and less on welfare assistance. Days of heroin and cocaine use in the prior month were remarkably similar in the different settings, although NAOMI participants reported spending significantly higher amounts on the purchase of drugs.

DISCUSSION

Analysis of the baseline characteristics of participants in the NAOMI trial demonstrates successful recruitment of the target population: long-term, chronic opioid injectors with severe health and social problems, and several previous addiction treatment attempts. In addition, almost all the participants are polydrug users with cocaine being the second most popular drug of choice, after heroin.

Vancouver participants had more severe problems when compared to Montreal participants in relation to unstable housing status, criminal activity, physical health status, and crack cocaine use. These characteristics have been persistently described as part of the environment in Vancouver's DTES from where the NAOMI participants were recruited.[9,48–50] Conversely, the Montreal site recruited younger injection drug users who partook in more life-threatening and risk behaviors like overdoses and injection equipment sharing, even after adjusting for age and injected cocaine use. It has been previously reported that there is a higher proportion of injection equipment sharing and overdoses in Montreal compared to Vancouver.[8,51] Broad implementation of harm reduction measures such as a decentralized needle exchange and a supervised injection facility in Vancouver may contribute to lower levels of risky injection practices. On the other hand, Montreal participants have received more psychological treatment than Vancouver and have been on MMT more times. While Vancouver has seen a more rapid expansion in availability of MMT over the past 15 years than Montreal, many of the methadone programs include minimal levels of psychological supports, whereas these are standard components of MMT in Montreal. Number of MMT attempts may differ in the two cities as well because of the differences in treatment delivery systems with Montreal having both maintenance and short-term MMT available, the latter being focused on providing opportunities for physical health assessment, counseling, and referral to community resources such as housing. British Columbia is the only province in Canada which allows methadone clinics to charge user fees, and this may result in a barrier to treatment re-entry for some former MMT patients.

NAOMI participant profiles are a well-suited target population for HAT. The Canadian sample shows similarities with the other studies in relation to drug use and treatment history, employment and legal status, and health (Table 4). However, NAOMI participants have a higher proportion of females, have poorer housing, have less support from welfare assistance, and spend more money on drugs than participants in all other HAT studies at baseline.

In the international literature related to opioid dependence, the expected ratio of females to males is usually 1:4.[52] However, the NAOMI study featured a higher ratio, almost 2:3, without differences between cities. At least in Vancouver, this is consistent with the literature; the proportion of women in MMT in British Columbia is 34.8%,[25] 36.3% in the Supervised Injection Facility Cohort,[53] and 48.8% in a cohort of illicit opioid users not in treatment.[54] In Montreal, the available data shows differences in the female proportion by study. For example, the OPICAN study had 19.8% females,[54] similar to the 16.7% of the St. Luc Cohort study with IDUs.[55]

TABLE 4 Patient's employment/legal, health, and drug use data

Variable	CA *n*=251 [SD]	CH *n*=1,035 [SD]	NL *n*=174 [SD]	SP *n*=62 [SD]	DE *n*=540 [SD]
Age (mean) [SD]	39.7 [8.6]	31.5 [7.2]	38.5 [5.7]	37.2 [5.5]	35.9 [6.8]
Women	38.6%	28%	17.8%	9.7%	18.2%
Poor housing	72.9%	49%	13.8%	21%	36.1%
Employment/legal situation					
Illegal activities/ income prior month	73.3%	50%	70.1%	58.1%	78.1%
Illegal activities prior month (mean days)	15.1 [12.7]		12.4 [?]	9.8 [12.2]	22.6 [9.8]
Major source of support					
Employment	15.9%		8.1%		4.0%
Welfare/public assistance	36.3%		57.6%		48.8%
Illegal activities	36.7%		28.5%		27.7%
Health					
HIV	9.6%	15%	13.2%	40.3%	6.9%
HCV	62.9%	82%		93.5%	78.5%
MAP physical health (mean)	15.3 [7.2]		11.5 [7.6]	23.4 [12.8]	
Ever attempted suicide	32.3%		37.9%		39.7%
Methadone previous treatment (median)	3		2	3	
Drug use					
Years of Heroin use (mean)	13.9 [8.0]	10.5	15.9 [5.7]	19.7 [6.4]	13 [6.3]
Days heroin use prior month (mean)	26.5 [7.4]		25.9 [6.0]	23.9 [9.5]	26.5 [6.9]
Days cocaine use prior month (mean)	16 [12.6]		18.7 [10.2]	23.1 [9.8]	15.5 [11.5]
Money spent in drugs (CAN)	$2,346 [$3,342]		$1,459 [$1,211]	$1,476 [$1,203]	$1,941 [$2,516]

CA=Canada; CH=Switzerland; NL=The Netherlands; SP=Spain; DE=Germany
(?) Not specified in the publication

However, a study with patients of a low-threshold MMT, a clientele more similar to the NAOMI target population, had a proportion of 48.9% females.[56] It is very difficult to differentiate a selection effect (i.e., more women reached by these services) from an actual higher proportion of female chronic heroin users in the study sites in relation to the international literature. Either the biases are the same, or the figures in

this study are representing a truly higher proportion of female heroin chronic users, at least in Vancouver. The Montreal situation is less clear.

Housing status is a strong predictor of drug treatment outcome.[57] Precarious housing lowers the chances of recovery from addiction, facilitates high risk behavior, limits access to social and health services, and leads to poorer engagement in treatment.[57] Moreover, homelessness has been associated with mental and physical health problems as well as drug abuse.[57–61] Homeless people tend to inject drugs more than non-homeless drug users.[62,63] The housing situation in the DTES of Vancouver (from where the NAOMI sample was recruited) is no less than alarming and has been the subject of much debate.[49,50,64] The study shows that chronic heroin dependent individuals who are not reached by the addiction treatment system have urgent housing needs. Given the relationship between negative consequences from addiction and availability of secure affordable housing, all interventions should strive to address both problems for greatest efficacy.

Aside from local differences in the drug scenes between the two cities, it is important to note that, in both cities, the housing situation shows indicators of instability and vulnerability. For example, almost 50% of all participants were living at their current address for less than 4 months. Furthermore, Montreal participants tended to live with people with alcohol and drug problems, whereas the Vancouver participants tended to live alone. Both situations present challenges in the recovery process of drug-dependent people.

Another distinctive difference of the NAOMI sample is that the Vancouver site, in relation to the European HAT participant's baseline profile, had a significantly higher prevalence of crack use, a practice that remains rare across Europe[65] even in marginalized populations.[62,66] Cocaine use among opioid-dependent people has become a common practice.[67] While we have effective opioid addiction treatments, the lack of effective pharmacological approaches in the treatment of cocaine addiction jeopardizes opioid addiction treatment results,[23] given that the participants continue to be involved in criminal activities, health risk behaviors, and participate in the drug scene. Thus, cocaine use (in any form) among opioid-dependant people has become a significant problem for service providers. Evaluation of cocaine use among MMT patients does not show promising results, although results are better if accompanied by psychosocial therapy.[68–72] For example, a study with almost 400 MMT patients showed that at 18 months there was no change in cocaine use; however, cocaine powder and speedball use decreased, and smoking crack significantly increased.[73] Another recent study using contingency management showed that at 6 months follow-up visits participants that continued on methadone treatment, compared to those not in treatment, did not differ in their cocaine-dependence diagnosis.[74] On the other hand, cocaine use among Swiss HAT clients has been shown to be a predictor of nonresponse to treatment.[75] Those who continued cocaine use also used illicit heroin, continued to associate with the drug scene, and engage in criminal activities. Also, daily cocaine users tend to drop out earlier from treatment. Thus, the crack use scenario in Vancouver's DTES and the predominant use of cocaine in any form (85%) could be an important factor for NAOMI treatment outcomes and should be carefully evaluated.

This study presents the profile of a selected group of opioid-dependent people: adult, chronic heroin-injecting users for whom available treatments have failed repeatedly in the course of their substance dependence. Participant's past or current health status and social situation shows a predominance of indicators of marginalization and social exclusion. The data presented here features the limitations of intentional sampling and cross-sectional studies. Thus, generalizations should be made

cautiously, and conclusions of causal relationships should be avoided. Nevertheless, this study provides a snapshot of those who have had a long "drug career" in opioid addiction and for whom the health care system has been unable to provide effective engagement. It also raises a special concern about the high stimulant use and the high level of social marginalization among this sample of opioid injectors.

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Exhibit ... referred to in the ... Affidavit of ... Dr. David Marsh ... sworn before me, this ... 25th ... day of ... May ... 2015 ... A COMMISSIONER FOR TAKING AFFIDAVITS

Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study

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ABSTRACT

Aims To identify dose-tapering strategies associated with sustained success following methadone maintenance treatment (MMT). **Design** Population-based retrospective cohort study. **Setting** Linked administrative medication dispensation data from British Columbia, Canada. **Participants** From 25 545 completed MMT episodes, 14 602 of which initiated a taper, 4183 individuals (accounting for 4917 MMT episodes) from 1996 to 2006 met study inclusion criteria. **Measurements** The primary outcome was sustained successful taper, defined as a daily dose ≤5 mg per day in the final week of the treatment episode and no treatment re-entry, opioid-related hospitalization or mortality within 18 months following episode completion. **Findings** The overall rate of sustained success was 13% among episodes meeting inclusion criteria (646 of 4917), 4.4% (646 of 14 602) among all episodes initiating a taper and 2.5% (646 of 25 545) among all completed episodes in the data set. The results of our multivariate logistic regression analyses suggested that longer tapers had substantially higher odds of success [12–52 weeks versus <12 weeks: odds ratio (OR): 3.58; 95% confidence interval (CI): 2.76–4.65; >52 weeks versus <12 weeks: OR: 6.68; 95% CI: 5.13–8.70], regardless of how early in the treatment episode the taper was initiated, and a more gradual, stepped tapering schedule, with dose decreases scheduled in only 25–50% of the weeks of the taper, provided the highest odds of sustained success (versus <25%: OR: 1.61; 95% CI: 1.22–2.14). **Conclusions** The majority of patients attempting to taper from methadone maintenance treatment will not succeed. Success is enhanced by gradual dose reductions interspersed with periods of stabilization. These results can inform the development of a more refined guideline for future clinical practice.

Keywords Methadone detoxification, methadone maintenance treatment, methadone tapering, opioid dependence, opioid substitution treatment.

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INTRODUCTION

Opioid dependence is a chronic, recurrent disease [1], and long-term patient maintenance on pharmacotherapeutic agents has been recognized as a key component of effective treatment [2]. Methadone maintenance treatment (MMT) is the most common and effective treatment for opioid dependence [3–5], and has been shown to improve health-related quality of life and protect against mortality while clients are engaged in treatment [6,7].

A randomized trial found MMT to be more effective in retaining individuals in treatment, reducing illicit drug use, drug-related human immunodeficiency syndrome (HIV) risk behaviours and illegal activity than long-term detoxification [8]. Systematic reviews of methadone detoxification have indicated that while withdrawal severity can be reduced, the majority of patients relapse to heroin use [9], although success is more likely with additional psychosocial care [10]. In fact, very few patients complete the process of tapering from MMT

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[11–15], and relapse is common among those who do reach a state of abstinence [16]. Despite widespread indications for long-term maintenance and largely negative results for detoxification, whether by patient or physician choice, methadone detoxification and dose tapering among maintained clients is observed commonly worldwide [17–19]. Individuals may choose to detoxify due to unrealistic expectations for recovery, pressure from family members or others, the social stigma associated with methadone, programme-related factors, factors associated with financial or travel restrictions and a desire to determine whether clients can cope without treatment [20]. Alternatively, physicians may choose to taper clients for disciplinary reasons or, in some jurisdictions, due to funding constraints or by standardized regulations on clinical practice.

Despite more than 40 years of experience and millions of clients served world-wide, a number of important questions regarding methadone dose-tapering strategies remain. Do the commonly recommended weekly taper guidelines, ranging from 5 to 10% [21–23], achieve optimal outcomes? Should a constant rate of tapering be maintained throughout the tapering process? Rather than considering only the rate of tapering, is the time from treatment episode initiation and the duration of the taper important?

The sparse evidence available provides little insight into effective dosing strategies or other predictors of success. A randomized trial of 63 MMT clients in rapid (10% of initial dose per week) versus gradual (3% of initial dose per week) methadone tapering found gradual tapering to be more effective [24]. Several other short-term and small-sampled studies identified the length of time in opioid replacement treatment, sustained abstinence from illicit drug use during treatment, vocational/financial stability, social stability (socialization with non-drug users) and strong motivation to detoxify as factors associated with successful tapering [25–27], although there was wide variation in outcome measurement across studies. A more recent study of 30 maintained clients found no successful methadone tapers, 20 clients stopped their tapers due to drug relapse or medical instability, and 10 remained in treatment over a maximum 41 months of follow-up [12].

Questions regarding clinical guidance for methadone tapering remain unanswered due, in part, to a lack of available longitudinal data and feasibility of long-term experimental studies. Population-level analysis of dosing dynamics during MMT episodes is facilitated in British Columbia (BC), Canada by a centralized medication dispensation database covering the entire province [18,28]. Methadone is recommended to be delivered with a maintenance-oriented philosophy in BC. Treatment is provided by specially licensed physicians in office-based settings or specialized drug treatment centres, some offering additional psychosocial care. In most cases, medication is dispensed and consumed at community pharmacies under direct supervision. The general ineffectiveness of detoxification treatment is recognized [29], and penalization of patients who relapse into illicit opioid use as well as voluntary withdrawal is discouraged. BC Provincial guidelines for dose tapering recommend a gradual taper at no more than 5% of initial dose per week [21,30].

Our objective was to identify methadone dose-tapering strategies associated with sustained success in terms of health and treatment outcomes following maintenance treatment. We conduct a population-level study of methadone clients in British Columbia, Canada to fulfil this objective.

METHODS

Patient population

This study utilized data from the BC PharmaNet database, which records all prescription medication dispensation in the entire province of BC. The cohort was selected from all individuals receiving methadone maintenance treatment (MMT) over an 11-year period: 1 January 1996–31 December 2006. Methadone prescribed for opioid dependence was distinguished from prescriptions for pain indications by separate drug identification numbers in the data set. Data fields available included a de-identified patient ID, date of birth, gender, drug identification number, the date of the prescription ('date'), the length of the prescription ('number of days supplied', or 'days'), medication dosage ('quantity'), de-identified prescriber code and pharmacy code, as well as a geographical identifier, aggregated by local health area. Data on hospitalizations from the BC Ministry of Health Discharge Abstract Database (dates and most responsible diagnoses of hospitalizations) and Vital Statistics (dates and causes of death) were linked to this database throughout the period of study follow-up through Population Data BC [31]. The study was approved by the University of British Columbia/Providence Health Care Behavioural Research Ethics Board.

Measures

Episode definition

MMT episodes were the focal point of our analysis. These were constructed using the 'service date' and 'days supplied' fields; a treatment episode length was calculated as the difference between the last and first days of dispensed medication {episode length = $[(\text{date}_{t1} + \text{days}_{t1}) - \text{date}_{t0}]$}, where t_0 is the date of

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episode initiation, t_1 is last date of service and $days_{t1}$ is the duration of the dispensation at time t_1 within a period of continuous retention in treatment, entailing no interruptions in prescribed doses lasting longer than 30 days. We considered all MMT episodes beginning after 31 January 1996 to ensure consistency in our calculation of episode lengths and eliminate left-censored observations. We focused our analysis on completed treatment episodes, thus also excluding right-censored observations. Efforts were made to correct any misclassification in the data set with regard to prescribed doses, lengths and dates of prescriptions. Fewer than 1% of identified errors could not be corrected.

Taper definition and study selection criteria

Consistent with previous research [18], periods of dose tapering were identified by examining changes in the mean daily dose per week (mean dose: $\sum_{i=1}^{J} \frac{quantity_i}{days_i} \Big/ J, J \leq 7$) during the course of each episode. The onset of the tapering period was defined as first instance, after the 12-week point, where the weekly dose decreased and remained at or below this lower level for at least 4 weeks [$dose_{t-i} < dose_t \leq dose_{t+i}$, i = (1, . . . ,4)]. This method was chosen to eliminate the possibility of misclassification of taper initiation as a result of dose titration, vacation catch-up prescriptions, database errors or otherwise. Further, preliminary analysis indicated that many episodes with an observed initiated taper were either reversed or reverted to a stabilized dose. In such cases, in the absence of information of patient or physician intentions (i.e. maintenance dose adjustment or intended taper) we selected completed episodes in which the mean dose was either decreasing over the final 4 weeks of the episode or had decreased to ≤5 mg per day during this period {included if (i) [(mean $dose_{t-3}$ − mean $dose_T$)/mean $dose_T$] < 0; or (ii) mean $dose_t$ ≤5 mg, where t = (t–3, t–2, t–1, T) and T is the terminal week of treatment}. The durations of tapers were therefore a minimum of 4 weeks.

Sustained successful taper definition

Given that an administrative data source was used, information regarding opioid use beyond the conclusion of treatment episodes was not available, resulting in potential outcome misclassification. We therefore constructed a multi-attribute proxy measure, defined as 'sustained success in tapering' using all available linked administrative data. As successful dose tapering is only the initial requirement towards the ultimate goal of indefinite opioid abstinence [32,33], this measure of sustained success featured four criteria: (i) methadone dose tapered to ≤5 mg/day in the final week of treatment, and within 18 months of treatment: (ii) no treatment re-entry; (iii) no drug-related hospitalization; and (iv) no mortality. The 18-month reference period was chosen based on distributions of time to treatment re-entry, to capture the majority of re-entries following successful tapering while maintaining sufficient patient follow-up.

Explanatory variables

As dose control is ultimately at the discretion of the physician, we were specifically interested in how dosing practices influenced the odds of sustained taper success. To this end, individual plots of weekly dose-tapering trajectories were inspected visually to inform construction of relevant covariates capturing dose changes during the tapering period. A set of five covariates were constructed: (i) the taper start week [number of weeks since treatment episode initiation, defined as: mean $dose_t$ < (mean $dose_{t-1}$, . . . , mean $dose_{t-4}$); mean $dose_t \geq$ (mean $dose_{t+1}$, . . . , mean $dose_{t+4}$); $t \geq 12$ weeks]; (ii) the total duration of the taper, from the taper start week to the end of the treatment episode (in weeks); (iii) the median rate of dose change throughout the duration of the taper [taper change rate = median $\left[\left(\frac{mean\ dose_t - mean\ dose_{t-1}}{mean\ dose_{t-1}}\right) * 100\right]$, t = (taper start week, . . . , episode end week)]; (iv) the median rate of dose change during weeks in which the dose was decreasing throughout the duration of the taper (i.e. taper change rate when $(mean\ dose_t - mean\ dose_{t-1}) < 0$); and (v) the percentage of weeks during which the dose was decreasing throughout the duration of the taper.

Other covariates, added to control for potential confounding, included the maximum mean dose per week (maximum dose) during the treatment episode, treatment adherence [the percentage of missed doses during the treatment episode: $\left(adherence = \frac{\sum_{i=1}^{T} days_i}{episode\ length}\right)$, where T = max (episode length)], age, gender, episode count, calendar year of episode initiation and individuals' Charlson Comorbidity Index (CCI) score [34], based on hospitalizations during the period 6 months prior to treatment episode initiation. Continuous variables were categorized taking into account observed distributions, and with the intention of maximizing clinical interpretability.

Data analysis

Univariate analyses were conducted to identify variables for inclusion in multivariate models. Multivariate logistic regression analysis was used to identify independent factors associated with sustained success. As some individuals had repeated taper attempts, generalized linear

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mixed regression models, with logit link and binomial distribution, were also estimated to capture unmeasured individual-specific confounding. Due to the collinearity and conceptual overlap between dose taper dynamics variables (ii), (iii) and (iv–v), three separate multivariate regression models were estimated with covariates (i) and (ii), (i) and (iii) and (i), (iv) and (v), controlling for all other covariates. These sets of variables capture different aspects of the taper, and thus provide complementary evidence on appropriate means of tapering. The goodness-of-fit of these three model formulations were compared using Akaike's and Bayesian information criteria (AIC and BIC). All analysis was executed with SAS version 9.2.

RESULTS

From a total of 32 656 treatment episodes captured in the study, 25 545 were non-censored, from which 14 602 were identified as having initiated a taper at some point during the episode. Among these episodes, 4917 were decreasing or had decreased below 5 mg/day in the final 4 weeks of the episode, thus meeting study inclusion criteria, and ended prior to 1 July 2005, thus allowing 18 months follow-up to verify our definition of sustained success. These episodes were counted among 4183 unique individuals.

From the study sample of 4917 treatment episodes, 1305 (27%) episodes were completed with a daily dose ≤5 mg/day; however, among episodes reaching this criteria, 659 were followed by at least one of the following events: treatment re-entry within 18 months (458 episodes, 35.1% of all completed tapers), opioid-related hospitalization [319 (24.4%)], mortality [29 (2.2%)]. As such, 1305 – 659 = 646 episodes (13% of the study sample) were defined as sustained successful tapers.

Summary statistics stratified by treatment outcome are presented in Table 1. Individuals with treatment episodes resulting in a sustained successful taper were younger, more likely to be male, had lower CCI scores, better treatment adherence, lower maximum mean weekly doses and longer taper durations.

Results of multivariate analyses on the odds of sustained success in the three models tested are presented in Table 2. Patient demographics and treatment adherence variables were included in each model, and their effects were largely consistent across model formulations. Individuals aged 25–34 and 35–49 years had 27–40% lower odds of sustained success in tapering compared to individuals younger than 25 years. Females also had lower odds of sustained success, with the most conservative estimated odds ratio (OR) suggesting 19% lower odds of sustained success compared to males [model 3: OR: 0.81; 95% confidence interval (CI): 0.67–0.99]. Individuals with higher levels of medical comorbidity also had lower odds of sustained success in tapering; however, this effect was not statistically significant in model 2, when tapering dynamics were represented with the taper duration [0.83 (0.68–1.00)]. Later subsequent treatment episodes had lower odds of sustained success, while episodes initiated in more recent calendar years, controlling for all other measured covariates, had higher odds of sustained success in tapering.

Treatment adherence was included in each of the model formulations, and was associated positively with higher odds of sustained success. Our results suggest that a 1% increase in adherence resulted in a minimum 1.9% increase in the odds of success [model 2: 1.02 (1.00–1.03)].

Results of model 1 suggest that individuals reaching a maximum dose of between 60–100 mg and more than 100 mg had 44 and 60% lower odds of sustained success in tapering compared to those maintained on lower doses. Univariate results were similar to those obtained in the multivariate model. An early taper start week (before week 12) had higher unadjusted odds of sustained success; however, the adjusted effect was not statistically significant. Finally, more aggressive tapers had lower odds of sustained success, as episodes with median percentage decreases greater than 4% were nearly 27% less likely to result in sustained success [0.73 (0.61–0.88)] in comparison to less aggressive tapers.

Model 2 indicated that taper duration was associated strongly with sustained success. Episodes in which the taper lasted 12–52 weeks were 3.58 times more likely to result in sustained success than those lasting <12 weeks [3.58 (2.76–4.65)], while tapers lasting longer than 52 weeks were 6.7 times more likely to result in sustained success [6.68 (5.13–8.70)].

Model 3 provides a refinement of model 1 results, indicating that tapers with 25–50% of weeks where the dose was decreasing had the highest odds of success [1.61 (1.22–2.14)]. In weeks during which the mean dose was decreasing, a median percentage change <5% had lower odds of success [0.53 (0.41–0.71)] than episodes in which the median percentage change was 5–15%, while higher percentage changes in mean dose when the dose was decreasing did not have statistically significantly different odds of sustained success.

Of the three models tested, model 2, with taper dynamics represented by the taper duration covariate, provided the highest AIC and BIC values, indicating greatest model fit and thus highest explanatory power. Each model formulation was tested using a generalized linear mixed regression model; however, given the low number of repeated taper episodes, results using this type of model were identical to the pooled analysis presented.

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Table 1 Summary statistics.

	Taper with sustained success[a]	*Unsuccessful taper*
	(n = 646)	*(n = 4271)*
CCI score mean (SD)	0.04 (0.43)	0.16 (0.93)
Episode no., median (IQR)	1 (1, 2)	1 (1, 2)
Calendar year, median (IQR)	5 (4, 6)	5 (3, 7)
% Treatment adherence[b], median (IQR)	96.4 (91.8, 98.5)	94.7 (88.6, 97.5)
Taper start week, median (IQR)	19 (13, 37)	22 (14, 38)
Female, no. (%)	184 (28)	1464 (34)
Age, no. (%): <25	162 (25)	728 (17)
25–34	217 (34)	1573 (37)
35–49	231 (36)	1737 (41)
≥50	36 (6)	233 (5)
Maximum dose, no. (%)[c]: <60 mg per day	247 (38)	1040 (24)
60–100 mg per day	287 (44)	2114 (50)
>100 mg per day	112 (17)	1117 (26)
Taper length, no. (%): <12 weeks	88 (14)	1829 (43)
12–52 weeks	238 (37)	1303 (31)
>52 weeks	320 (50)	1139 (27)
% change in dose, no. (%): <1%[d]	327 (51)	1909 (45)
1–4%	81 (13)	548 (13)
>4%	238 (37)	1814 (42)
% change in dose when decreasing, no. (%): <5%	65 (10)	695 (16)
5–10%	283 (44)	1567 (37)
10–15%	154 (24)	883 (21)
>15%	144 (22)	1126 (26)
% weeks dose decreased: <25%	79 (12)	665 (16)
25–50%	230 (36)	1094 (26)
50–75%	176 (27)	975 (23)
75–90%	75 (12)	397 (9)
>90%	86 (13)	1140 (27)

[a]Defined as an episode in which the daily dose in the final week is ≤5 mg/day, and within 18 months of episode completion, the individual does not re-enter treatment, is not hospitalized for a drug-related cause and does not suffer mortality. [b]Percentage of days received medication during treatment episode. [c]Maximum mean weekly dose through duration of treatment episode. [d]Median percentage change in mean weekly dose throughout duration of taper. CCI: Charlson Comorbidity Index; IQR: interquartile range; SD: standard deviation.

DISCUSSION

We designed our analysis to inform the development of improved clinical practices for methadone dose tapering. Cumulatively, the results of our multivariate analyses suggest that longer tapers had substantially higher odds of success, regardless of how early in the treatment episode they were initiated, and a more gradual tapering schedule with dose decreases scheduled in only 25–50% of the weeks in treatment provided the highest odds of sustained success in tapering. These results provide a more refined and informative guideline for future practice. However, these results, and methadone dosing guidelines in general, are intended to supplement physician decision-making, rather than replace it. While patient and physician decision-making were not observed in the database, and although such actions were discouraged in clinical guidelines, one might speculate that the more aggressive tapers were disciplinary in nature. Regardless of the reason for such tapers, it is clear that outcomes are substantially poorer in such cases. Conversely, episodes with more gradual tapering, resulting in higher odds of success, may be indicative of individualized care, with doses titrated and tapered according to individual needs in suppressing withdrawal symptoms: a practice which is widely recommended [2,20–22].

While we have characterized dose-tapering strategies with higher odds of sustained success, the overall rate of success was just 13% among episodes selected for this analysis, 4.4% (646 of 14 602) among all episodes initiating a taper, and 2.5% (646 of 25 545) among all completed episodes in the data set. These poor outcomes are consistent with the findings of previous analyses [9–15], and are observed despite the frequency with which tapers are observed in BC, contrary to clinical guideline recommendations. Further, longer duration of exposure in treatment is associated with improved post-treatment

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Table 2 Results of multivariate regression analysis of sustained success in dose tapering.

	Unadjusted odds ratios	*Adjusted odds ratios*	*Adjusted odds ratios*	*Adjusted odds ratios*
		Model 1	*Model 2*	*Model 3*
Covariate	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
Age : <25	Ref	Ref	Ref	Ref
25–34	0.62 (0.50–0.77)	0.71 (0.56–0.89)	0.78 (0.61–0.98)	0.72 (0.57–0.91)
35–49	0.60 (0.48–0.74)	0.69 (0.55–0.87)	0.76 (0.60–0.96)	0.70 (0.55–0.89)
≥50	0.69 (0.47–1.03)	0.71 (0.47–1.06)	0.79 (0.52–1.21)	0.74 (0.49–1.12)
Gender: male	Ref	Ref	Ref	Ref
Female	0.76 (0.64–0.92)	0.79 (0.65–0.95)	0.75 (0.61–0.91)	0.81 (0.67–0.99)
CCI score	0.75 (0.62–0.91)	0.82 (0.67–0.99)	0.84 (0.69–1.03)	0.82 (0.67–1.00)
Episode no.	0.71 (0.64–0.78)	0.72 (0.65–0.80)	0.73 (0.65–0.81)	0.73 (0.66–0.81)
Calendar year	1.03 (0.99–1.07)	1.08 (1.04–1.13)	1.09 (1.05–1.15)	1.07 (1.02–1.12)
Treatment adherence[a]	1.04 (1.03–1.05)	1.04 (1.02–1.05)	1.02 (1.00–1.03)	1.03 (1.03–1.05)
Maximum dose[b]: <60 mg per day	Ref	Ref		Ref
60–100 mg per day	0.57 (0.48–0.69)	0.56 (0.46–0.67)	0.46 (0.37–0.56)	0.58 (0.48–0.71)
>100 mg per day	0.42 (0.33–0.54)	0.39 (0.31–0.51)	0.31 (0.23–0.40)	0.43 (0.33–0.55)
Taper start week	1.28 (1.03–1.59)	1.01 (1.00–1.01)	1.00 (1.00–1.00)	1.00 (1.00–1.01)
Taper length: <12 weeks	Ref		Ref	
12–52 weeks	3.80 (2.94–4.90)		3.58 (2.76–4.65)	
>52 weeks	5.84 (4.56–7.48)		6.68 (5.13–8.70)	
% change in dose: <1%[c]	Ref	Ref		
1–4%	0.86 (0.67–1.12)	0.77 (0.59–1.01)		
>4%	0.77 (0.64–0.92)	0.73 (0.61–0.88)		
% change in dose when decreasing: <5%	0.52 (0.40–0.69)			0.53 (0.40–0.71)
5–15%	Ref			Ref
15–35%	0.75 (0.60–0.93)			1.03 (0.82–1.31)
35–50%	0.70 (0.43–1.16)			1.42 (0.83–2.43)
>50%	0.42 (0.18–0.97)			1.12 (0.47–2.67)
% weeks dose decreased: <25%	Ref			Ref
25–50%	1.77 (1.35–2.33)			1.61 (1.22–2.14)
50–75%	1.52 (1.14–2.02)			1.29 (0.96–1.73)
75–90%	1.59 (1.13–2.23)			1.32 (0.92–1.87)
>90%	0.63 (0.46–0.87)			0.56 (0.40–0.79)
AIC	–	3631.82	3485.36	3569.91
BIC	–	3714.14	3548.12	3684.65

Ref: reference group; 95% CI: 95% confidence interval; AIC: Akaike's information criterion; BIC: Bayes information criterion; CCI: Charlson Comorbidity Index. [a]Percentage of days received medication during treatment episode. [b]Maximum mean weekly dose through duration of treatment episode. [c]Median percentage change in mean weekly dose through duration of taper. Blank cells indicate that the variable was not included in the specified multivariate regression model.

outcomes such as reduced opioid use, reduced criminal activity, improved social productivity and reduced risk of mortality [29,35–38]. While our focus in this paper has been on the technical aspects of therapeutic tapering, there a number of reasons why methadone maintenance clients may wish to achieve a drug-free state in the process of recovery from drug use [32,33]. However, the high risks of drug relapse and adverse health outcomes need to be communicated to clients choosing to do so. In light of these risks, an informed consent process should be considered by regulatory bodies before initiating a tapering schedule.

The negative relationship between the maximum, or maintenance, dose, as well as results of later subsequent taper treatment episodes and the probability of success need to be interpreted carefully. A recent Cochrane Review of dosing in MMT programmes concluded that clients receiving maintenance doses of 60–100 mg per day were retained in treatment longer than those on lower doses [39], while a previous analysis of this data set confirmed this result and found maintenance doses >100 mg/day were associated with longer retention in treatment [28]. Clinical guidelines in BC instruct physicians to use discretion, and work with patients to provide individualized care in identifying a suitable dose which eliminates withdrawal symptoms and drug craving. That said, physician decision-making was not observed, and methadone dose is often determined by the policies of

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individual practices. In cases where doses were titrated to individuals' needs, those requiring higher daily doses could be considered to have higher addiction severity requiring a higher maintenance dose and, perhaps not surprisingly, had lower odds of successfully tapering. Although the relationship between the maintenance dose and a prior drug use severity is not observed and therefore not testable in our data set, the notion that higher a priori drug use severity decreases the likelihood of successful transition to abstinence is supported in the available literature [40,41].

Strengths and weaknesses

There are notable limitations that are important to consider when interpreting results of this study. First, the outcome we have constructed based on the data available to us is a proxy of sustained abstinence, and cannot capture those who revert to illicit opioid use without returning to treatment or experiencing the adverse health outcomes included in the outcome. What is being assessed is therefore more indicative of medical safety and patient stability following treatment rather than drug relapse. Further study is needed to confirm these results prospectively and potentially over longer time-frames. Secondly, due to the nature of the data set, physician decision-making was not observed, which required us to classify stages of the methadone treatment episodes, particularly the point of initiation of a taper, according to observed changes in doses. This needs to be considered carefully in further research and practical application. Thirdly, any non-experimental study may be subject to residual and/or unmeasured confounding [42]—in our case, we could not observe whether clients were primarily users of heroin or prescribed opioids, addiction severity, treatment setting (office-based versus drug treatment centre) or availability of additional psychosocial care and other potential confounders. In a separate analysis, we used the random-effects frailty term from a previous analysis on the time to discontinuation of repeated methadone treatment episodes as an additional covariate in each model to determine the potential effects of individual-level unmeasured confounding. Results were similar to those presented, with only minor differences in the magnitude of effect sizes. However, we are careful not to interpret the tested relationships as causal, as these unobserved factors may confound or modify the effects of dose changes on sustained success. Finally, the results in the current study represent outcomes of practices in BC, Canada where treatment is heavily subsidized, a maintenance-oriented philosophy persists and office-based treatment is available. In other settings, barriers due to financial constraints or availability may impact clinical practice and compromise treatment outcome.

The advantages of using this data set, however, were substantial: availability of a centralized drug dispensation database allowed for a population-level study of methadone dose tapering among maintained clients unparalleled in size. The large sample size and level of detail in methadone dosing allowed us to classify and compare dose-tapering strategies, providing new insights into clinical practice. We are hopeful that this study will spur further research on tapering strategies for clients in opioid substitution treatment programmes wishing to achieve a state of opioid abstinence.

Declarations of interest

None.

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This is Exhibit D referred to in the affidavit of Dr. David Marsh sworn before me, this 25th day of May 20 15

A COMMISSIONER FOR TAKING AFFIDAVITS

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

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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.

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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
Trazadone	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 or more 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 at 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 should 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 of 100 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 chose 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

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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

SAMPLE

Appendix G Sample Physician/Pharmacist/Patient Agreement Letter

DR. XXXXXXXXXX
XXXXXXXXX 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: _____

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

Counselling/Clinical Notes:

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.

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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)

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