Methadone for Analgesia

KT Tools Project
Literature Search and Review for Online Training Tool

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ABBREVIATIONS AND ACRONYMS

CDC: Centers for Disease Control and Prevention
CPSBC: College of Physicians and Surgeons of British Columbia
CYP2B6: Cytochrome P450, Family 2, Subfamily B, Polypeptide 6
CYP2D6: Cytochrome P450, Family 2, Subfamily D, Polypeptide 6
CYP3A: Cytochrome P450, Family 3, Subfamily A
EAPC: European Association for Palliative Care
ECG: Electrocardiogram
EPCRC: European Palliative Care Research Collaborative
ESMO: European Society For Medical Oncology
FDA: Food and Drug Administration
FSH: Follicle Stimulating Hormone
GOPI: Global Opioid Policy Initiative
IAHPC: International Association for Hospice and Palliative Care
INCB: International Narcotics Control Board
IV: Intravenous
LH: Luteinizing Hormone
LTOT: Long-Term Opioid Therapy
MMT: Methadone Maintenance Therapy
NCCN: National Comprehensive Cancer Network
NHS: National Health Service
NMDA: N-methyl-D-aspartate
NOUGG: National Opioid Use Guideline Group
PAR: Parenteral
PO: Oral
TdP: Torsades De Pointes
WHO: World Health Organization

FOREWARD

This literature review provides an update of peer-reviewed literature published on methadone use for cancer and chronic non-cancer pain, commonly reported adverse effects, and important findings surrounding methadone formulary availability. An overview of methadone use regulation in Canada and select developed countries is provided. In addition, the use of methadone for analgesia in pediatric patients and opioid-dependent patients is discussed.

METHODS

A comprehensive literature search for peer-reviewed studies and reviews that investigated the use of methadone for analgesia was undertaken. A Medline (PubMed) search was performed on May 6, 2014 with different search queries. The Medline search was limited to articles published from January 1, 2004 until present. Studies for which the abstracts are unavailable on Medline or the reports were written in any language other than English were excluded from further analysis. Animal studies were excluded.

Table 1. Summary of Medline search for peer-reviewed studies on methadone for analgesia performed in May 2014

Search	Query	No. of peer-reviewed publications
1	Search ((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date – Publication])	1070
2	Search (((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT cocaine	1017
3	Search ((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT cocaine)) NOT addiction	955
4	Search ((((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT	125

	cocaine)) NOT addiction)) AND palliative	
5	Search ((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication])))) NOT cocaine)) NOT addiction)) AND cancer	167
6	Search ((((((((methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) NOT cocaine) NOT addiction) AND palliative) AND cancer) AND (“2004/01/01”[Date – Publication] : “3000”[Date – Publication])	77
7	Search ((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication])))) NOT cocaine)) NOT addiction)) AND non-cancer	10
8	Search ((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication])))) NOT cocaine)) NOT addiction)) AND chronic pain	124
9	Search ((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT	178

	maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT cocaine)) AND review	
10	Search ((methadone) AND guidelines) AND ("2004/010/0"[Date - Publication] : "3000"[Date - Publication])	187
11	Search (((methadone) AND pain) AND guidelines) AND ("2004/01/01"[Date - Publication] : "3000"[Date – Publication])	59
12	Search (((methadone) AND pain) AND guidelines) AND cancer	36
13	Search ((((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT cocaine)) NOT addiction)) AND palliative)) AND Canada	14
14	((methadone) AND license) AND Canada	0
15	((methadone) AND policy) AND Canada	40
16	Search ((((((((((((Methadone) NOT substance) NOT abuse) NOT abusing) NOT dependence) NOT maintenance) AND ("2004/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT	5

	cocaine)) NOT addiction)) AND palliative)) AND pediatric	
17	((methadone) AND exemption) AND Canada	1
18	(methadone) AND end-stage renal disease	17
19	methadone province Canada NOT China NOT Vietnam NOT addiction NOT dependence	4
20	Search ((methadone) AND substance misuser) AND cancer pain	2
21	Search ((methadone) AND substance misuser) AND pain	39

Shared documents available at Palliativedrugs.com were searched for any reference to methadone, methadone for analgesia and methadone in palliative care/end-of-life care. In addition, general opioid protocols were viewed if applicable to methadone for cancer pain in palliative patients. Guideline or specific opioid protocols were excluded if a word search for "methadone" did not have any hits.

CHAPTER 1: METHADONE OVERVIEW

This chapter provides an overview of methadone use, pharmacokinetics, and bioavailability. The advantages and disadvantages of this alternate opioid are discussed.

Methadone was originally developed in Germany and has been used as an analgesic since the mid-1940s. Its use in treating opioid addiction was first reported in 1965 (Watanabe, 2001). Methadone has had resurgence for use in the management of cancer pain and chronic non-cancer pain, particularly if there is a neuropathic component (Brown et al., 2004). However, concerns about safety when methadone is prescribed by inexperienced physicians weaken recommendations for methadone use in internationally recognized guidelines. In addition, a lack of randomized controlled trials and stigma surrounding opioid addiction may further act as a barrier to treating pain (Shaw and Diwan, 2010).

In 2000, the World Health Organization (WHO) and the International Narcotics Control Board (INCB) published a guideline entitled, *Achieving balance in national opioids control policy: guidelines for assessment*, to address the balance needed between drug use regulations that prevent abuse, misuse, and diversion, and experienced medical professionals that are able to provide opioids to patients living and dying with pain (WHO, 2000). Despite this dated global initiative, evidence suggests that access to adequate medication for patients with cancer pain and chronic non-cancer pain is still profoundly restricted by inadequate formulary availability and over-regulation (Cherny et al., 2010; Cleary et al., 2013).

Methadone for analgesia

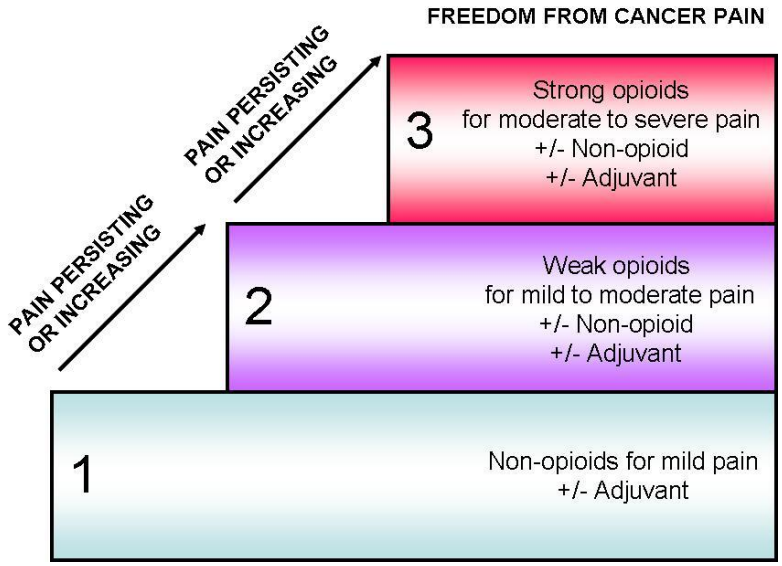
Methadone is synthetically derived and is commonly prescribed for the prevention of opioid-withdrawal symptoms and maintenance therapy in opioid-dependent patients. It has been increasingly recognized as an alternate and cost-effective analgesic for treatment of cancer pain and non-cancer pain in palliative patients. Importantly, methadone is often prescribed for patients that display opioid toxicity or are opioid-tolerant, or are allergic to, or are unable to tolerate the side effects of morphine or other strong opioids (Table 1.1) (Pollock et al., 2011). In addition, its analgesic efficacy in patients with renal failure and/or on dialysis is widely reported (O'Connor and Corcoran, 2012).

Table 1.1 Indications for methadone as an analgesic (modified from Toombs and Kral, 2005)

Cost
Morphine allergy or allergy to another first-line opioid
Neuropathic pain
Opioid adverse effects
Pain refractory to other opioids
Uncontrolled pain

According to the WHO analgesic ladder, pain may be classified as mild, moderate or severe, and appropriate analgesia is chosen according to pain severity (Figure 1.1; WHO, 2002). Step 3 strong opioids now used for the management of cancer pain in adults include fentanyl, hydromorphone, methadone, morphine, and oxycodone. When pain can not be controlled with one first-line opioid despite adequate dose titration, or when adverse effects become intolerable, pain is often managed by switching to another first-line opioid.

Figure 1.1 The WHO analgesic ladder for cancer pain in adults (modified from www.who.int/cancer/palliative/painladder/en/)



Oral methadone is included in the *2013 WHO Model List of Essential Medicines 18th list* and the *International Association for Hospice and Palliative Care (IAHPC) List of Essential Medicines for Palliative Care* (IAHPC, 2007; WHO, 2013)**.** Disadvantages of methadone use include unique pharmacokinetic properties that require accurate

measuring to avoid inadvertent overdose, stigma associated with addiction and street value.

Methadone pharmacokinetics and bioavailability

Methadone is a racemic mixture of L- and D-methadone enantiomers, each having distinct physicochemical properties. L-methadone is an analgesic and is 8–50 times more potent than D-methadone. D-methadone is an antitussive; it prevents reuptake of 3H-5-hydroxytryptamine and norepinephrine (Wheeler and Dickerson, 2000; Inturrisi, 2005). Methadone is an opioid agonist and an N-methyl-D-aspartate **(**NMDA) antagonist of NMDA receptors. NMDA receptors are associated with the amplification of neuropathic chronic pain and the development of opioid-tolerance.

Methadone has higher bioavailability than morphine or hydromorphone. Approximately 80%–90% of an oral methadone dose is absorbed and it appears in plasma within 30 min of administration. Tmax is approximately 4 h, and analgesic effects begin 1–2 h after administration (Zernikow et al., 2009). Methadone has an extended terminal elimination half-life (mean 20–35 h, range 5–130 h) and in general, steady-state is not achieved for approximately two weeks after initiation of therapy or changes in dosage (Overholser and Foster, 2011). The high bioavailability and lipophilicity of methadone, and consequent rapid absorption, allows it to be successfully used as rescue medication for breakthrough pain. However, these properties increase the risk of toxic accumulation in tissues if increased doses are given over a short period of time.

Methadone is primarily metabolized in the liver into inactive metabolites by cytochrome P450 enzymes (i.e. P450 CYP 3A4). In methadone-naïve individuals, it takes

approximately two weeks to convert methadone into inactive metabolites (Modesto-Lowe et al., 2010). Methadone is primarily excreted in feces, yet approximately 20% of unchanged methadone is excreted in urine (King et al., 2011). This dual elimination without active metabolites allows for safe use in patients with renal and liver failure (Pollock et al., 2011).

Importantly, methadone exhibits substantial interindividual pharmacokinetic variability and is associated with numerous drug interactions (Overholser and Foster, 2011). Therefore, use of methadone requires careful individualized dosing schedules (King et al., 2012; Caraceni et al., 2012).

Cost

Methadone is a cheap analgesic drug. It has long been proposed for use as a first-line opioid in developing countries where drug costs limit access to opioids (Bruera et al., 2004). A recent pilot study examining global availability, dispensing prices, and affordability of opioids indicates that apart from morphine (free in seven of 13 surveyed countries), solid oral methadone is the lowest-priced medicine, followed by the transdermal fentanyl patch (De Lima et al., 2014). In 2005, this translated into considerable monthly savings in a developed country such as the US, where prescription drugs are not often subsidized (Table 1.2; Toombs and Kral, 2005).

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(See Excel Sheet 1 for more references)

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CHAPTER 2: METHADONE IN CANADA AND SELECT DEVELOPED COUNTRIES

This chapter serves as an introduction to methadone use regulation in Canada. It will also provide an outline of existing regulation of methadone use for analgesia in Australia, Germany, New Zealand, the United Kingdom (UK), and the United States (US).

Canada's methadone use regulations

Prescribed use of methadone for maintenance therapy or analgesia in Canada is restricted under section 56 of the Controlled Substances and Regulations Act. Depending on the province or territory of residence, a physician may be exempt from these prescribing restrictions by Health Canada with endorsement from the physician's provincial or territorial licensing body or by direct application to Health Canada (the complete application process is described in *Methadone for analgesia: state assessment*). The Canadian National Opioid Use Guideline Group (NOUGG) has published guidelines for the use of methadone in chronic non-cancer pain (described in CHAPTER 4). However, uniform Canadian guidelines, recommendations, consensus statements, and best practices describing methadone use for cancer pain are lacking.

Evidence further suggests that few Canadian physicians are informed about or can prescribe methadone for analgesia (Hawley, 2012). As a result, options for pain management in home, hospice, or residential care settings are limited, particularly in rural settings. Lack of financial support and human resources are other commonly perceived

barriers to providing methadone as part of quality inpatient palliative care (Towns et al., 2012). Importantly, Canadian national statistics or data collected on the use of prescription methadone or other opioids for analgesia are minimal. Major and concerted Canadian policy initiatives are absent, and these require vastly improved national data indicators and monitoring to allow for and evaluate evidence-based interventions on prescription opioid use and misuse (Fisher and Argento, 2012).

- The majority of physicians in British Columbia, Canada, are uninformed about the use or advantages of prescribing methadone for a palliative patient and less than 10 % are licensed to prescribed methadone for analgesia. Major factors influencing the decision to apply for methadone prescribing exemption in B.C. include: need for exemption, lack of knowledge, 'too much hassle', college scrutiny, addiction risk, side effects, drug interactions, and electrocardiogram changes (Hawley et al., 2013)
- In Canada, methadone availability is limited to oral tablet or liquid suspension formulation. Both may prove problematic for palliative patients that have difficulty swallowing or that are unconscious. Methadone tablets may be more convenient and are less prone to measuring errors; however, they are more expensive that the oral suspension form in British Columbia (Hawley, 2012)
- In Ontario, Canada, prescription of methadone for analgesia is mostly provided by palliative care programs. However, considerable variability of available services exists between inpatient palliative care settings. Further financial support and

resources are required to ensure consistent high quality of care in both urban and rural areas (Towns et al., 2012)

- Many pediatric oncologists in North America lack experience and education in the use of methadone for cancer pain (Roth et al., 2013)
- After taking a course intended to improve Ontario physicians' opioid prescribing for patients with chronic non-cancer pain and to improve physicians' skills in identifying and managing opioid misuse and addiction, a marked reduction in the quantities of opioids prescribed was observed (Kahan et al., 2012)
- Methadone was implicated in approximately 15% of opioid-related deaths in Ontario, Canada between 2006 and 2008 (Madadi et al., 2013)

Methadone prescription

Methadone in Canada is most commonly prescribed in flavoured oral liquid form and is usually made up from powder in the dispensing pharmacy. It can be further diluted in water or any juice (except grapefruit) for enhanced palatability. These preparations require refrigeration, should not be frozen, and should always be shaken before use. Patients should use a syringe to measure the liquid methadone preparation. The tablet form of methadone (1 mg, 5 mg, 10 mg and 25 mg tablets) reduces the likelihood of dosing errors and may be preferred if patients' measuring skills are in doubt, or if the liquid methadone preparation cannot be easily or safely refrigerated (Dian and Hawley; on behalf of the College of Physicians and Surgeons of British Columbia [CPSBC], 2010).

Pharmacies can prepare custom-made methadone capsules or suppositories if standard preparations are not satisfactory, or when patients are unable to swallow or if doses are too high to allow buccal or sublingual administration (Dian and Hawley; on behalf of the CPSBC, 2010). See *Methadone for analgesia: state assessment* for drug compounding regulations).

Methadone for subcutaneous injection (Synastone®; 10 mg/ml) is available in Canada through the Special Access Program coordinated by Health Canada (see *Methadone for analgesia: state assessment*). Many regional palliative care units keep a supply of parenteral methadone available and may be able to supply other units when needed (Dian and Hawley; on behalf of the CPSBC, 2010).

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(See Excel Sheet 1 for more references)

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Methadone use in select countries

The following section provides and overview of methadone use for analgesia in Australia, Germany, New Zealand, the UK, and the US.

Australia

The Royal Australian College of Physicians (RACP) published guidelines in 2009 entitled, *Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use*. In Australia, the use of opioid drugs (morphine, methadone, and oxycodone) is mainly controlled by S8 legislation and several other schedules and laws in each jurisdiction. Prescribers providing chronic opioid treatment for individual patients or seeking to prescribe opioids to a recognized drug-dependent patient need prior approval from relevant government departments (RACP, 2009). In this way, State and Territory branches of pharmaceutical services can attempt to monitor use of opioids, coordinate supply to individuals, and identify drug seeking behaviour where a patient seeks opioids from more than one source (RACP, 2009). In addition, a patient may obtain Schedule 8 medication at a subsidized rate from Medicare Australia and the Pharmaceutical Benefits Scheme (RACP, 2009). It is necessary in some instances for the treating medical practitioner to advise the Pharmaceutical Benefits Scheme that they have complied with the relevant jurisdiction legislation such as obtaining a permit from the relevant heath department. In certain instances, the practitioner must affirm that the pain is severe, chronic and not responding to 'non-narcotic analgesics' (RACP, 2009). There are additional controls on the

prescription and/or dispensing of controlled drugs in particular jurisdictions (RACP, 2009).

Indication(s) for treatment and quantity of opioids dispensed for opioid prescription in Australia are not recorded (Huxtable et al., 2011). However, there has been a recent and significant rise in the total number of opioid prescriptions issued under the Australian Pharmaceutical Benefits Scheme (Leong et al., 2009), and methadone consumption (mg/capita) has steadily increased since 1980 (Pain and Policies Study Group, 2013). A recent nation-wide anonymous survey of 95 Australian palliative care specialists concluded that there is wide variation in practice for initiating methadone treatment in a palliative care setting, and there is no national consensus on the conversion ratio between oral and parenteral methadone. Some regional guidelines describe the use of methadone for analgesia in palliative care. For instance, the Northern Rivers Health Care Service *Palliative Care Pain Management Practice Guidelines* recommend methadone under specialist supervision for patients who develop opioid toxicity or renal failure (NRAHS, 2005). In addition, a significant number of specialists practicing palliative care medicine in Australia are using methadone in conjunction with other opioids rather than as the sole opioid treatment (Syrmis et al., 2014). In Australia, methadone is available in oral (tablet or liquid) or injectable form.

Germany

Germany saw a steady increase in methadone consumption (mg/capita) from 1980 to 2011 (Pain and Policies Study Group, 2013). A retrospective analysis of health insurance claims in Germany has reported an increase in opiate prescription for cancer

and chronic non-cancer pain, with a pronounced trend towards prescription of WHO Step 3 opioids, particularly in non-cancer patients (Schubert et al., 2013). However, prescription of levamethadone and methadone were excluded from this study. The formulary availability of opioid medication in Germany is approximately 69% (9 out of 13 possible opioid formulations were available at the time the survey was taken) (De Lima et al., 2014), and oral methadone is available at less than 25% of cost (Cherny et al., 2010). The frequency of long-term treatment of non-cancer pain with opioids is growing in Germany, despite controversy surrounding its benefit (Schubert et al., 2013). German S3 guidelines published in 2012 concluded that there is no sufficient scientific evidence for opioid treatment exceeding three months in duration for patients with chronic non-cancer pain; however, this statement has not been widely received (Schubert et al., 2013). Physicians practicing in Germany (family MDs, oncologists and surgeons) are not required to obtain a permit before prescribing opioids, and patients that are prescribed opioids do not need to be registered (Cherny et al.,2010). However, Germany does require duplicate or triplicate opioid prescriptions and special application forms (free). Opioid prescriptions are limited to 30 days' supply, and there is no methadone dose limit in Germany. Opioid medications are dispensed at no cost to patients through a health insurance fund, but patients are required to pay a fixed dispensing fee (De Lima et al., 2014).

New Zealand

New Zealand opioid regulations differ between the prescription of opioids for analgesia and for addiction. There are no restrictions on prescribing opioids for pain

management and any registered doctor may prescribe any amount of any opioid for an unlimited period of time. Prescription of opioids for the treatment of opioid dependence, however, is tightly controlled and only physicians working for a formally recognized addiction treatment service may initiate prescription for the treatment of dependence. Very few physicians are individually authorized in this capacity (RACP, 2009). Once treatment is initiated, other physicians may be authorized by the original prescribing physician to continue the prescription and this authorization is required on an individual patient basis (RACP, 2009). Authorization usually defines maximum dose and the conditions of dispensing, and must be renewed three monthly. There is no registration of individuals receiving treatment with any central authority (RCAP, 2009).

Methadone consumption (mg/capita) in New Zealand has had considerable annual variation since 1980 (Pain and Policies Study Group, 2013). Prescription opioid drug abuse has been a long-standing issue in New Zealand, as imported heroin became increasingly uncommon and virtually unavailable for "street" supply approximately 30 years ago. As such, prescription opioids (buprenorphine, morphine and methadone) have become a prime source (Robinson et al., 2011). Nonetheless, the availability of opioid medication in New Zealand is approximately 69% (9 available formularies out of a possible 13). Furthermore, New Zealand had the best opioid affordability (nine medications/formulations available for free); opioid dispensing is free as well (De Lima et al., 2014). Methadone is available in oral (tablet or liquid) or injectable form.

UK

Methadone use in the UK is regulated by the Misuse of Drugs Act. It allows for the prescription and administration of controlled drugs by medical practitioners as well as for the development of regulations on the control and prescription monitoring of controlled drugs. The cost of opioids in the UK is varied. In Edinburgh for example, opioids are free, but not in Leeds (De Lima et al., 2014). Methadone is available at less than 25% of cost (Cherny et al., 2010).

Physicians (family MDs, oncologists and surgeons) are not required to obtain a permit before prescribing opioids, and patients prescribed opioids do not need to be registered (Cherny et al., 2010). Duplicate or triplicate opioid prescription forms are required, but no special form is needed. The maximum number of days supplied on one opioid prescription for pain is 28 days (Cherny et al., 2010). Importantly, both nurses and pharmacists in the UK may issue a limited prescription for opioids in an emergency situation. Furthermore, the UK is one few European countries that allow physicians to prescribe opioids by telephone or to fax a prescription to the pharmacist. The country also allows pharmacists to correct technical errors on opioid prescriptions (Cherny et al., 2010).Oral (tablet and liquid) and injectable methadone is available in the UK.

The UK saw a steady increase in methadone consumption (mg/capita) from 1980 to 2011 (Pain and Policies Study Group, 2013). However, methadone is not included in the UK National Institute for Health and Clinical Excellence (NICE) 2012 guidelines entitled, *Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults*. Details on methadone use for cancer pain are further excluded from the National Health Service (NHS) Quality Improvement Scotland and

Scottish Intercollegiate Guidelines entitled, *SIGN 106 Control of pain in adults with cancer* (NHS, 2008). However, several independent guidelines (shared on Palliativedrugs.com) from palliative hospices in the UK describe the use of methadone for analgesia in cancer pain and chronic non-cancer pain. In 2007, methadone was only indicated as an alternative to alfentanil, fentanyl and buprenorphine in patients with moderate to severe cancer pain with renal impairment (Ward and Edwards, 2007). Since then, methadone has gathered several indications. It is indicated as a third line analgesic for moderate to severe malignant nociceptive pain, pain relief in renal failure, morphine allergy, neuropathic chronic non-cancer pain, and as an antitussive agent (Gannon, 2011). Furthermore, it is considered specifically appropriate for neuropathic pain and for patients with intolerance of, or lack of response to other opioids (Twycross and Wilcock, 2008; Rowans Hospice, 2009).

In a survey all palliative care consultants in the Northern Deanery, United Kingdom, 14 of 29 consultants frequently prescribed methadone for pain. When patients were no longer able to swallow oral methadone, practice varied. Concerned about the potential for skin reactions at the site of methadone injections, three consultants (21%) reverted to an alternative opioid given subcutaneously. Ten of these (71%) used subcutaneous methadone, because alternative opioids had been ineffective or intolerable in the past (Porteus et al., 2013).

US

US physicians have increasingly used methadone as a treatment for chronic non-cancer pain since the mid-1990s (Centers for Disease Control and Prevention [CDC],

2012). The increased use of methadone observed since 1999 may be due to growing costs of treating pain with opioids and increasing reports of abuse of other, more expensive, extended-release opioids (CDC, 2012).

Methadone is listed on schedule II of the Controlled Substances Act in the US. Since 1976, all physicians with appropriate Drug Enforcement Agency registration are allowed to prescribe methadone for analgesia (Toombs and Kral, 2005). State laws vary regarding this documentation requirement and not all pharmacies stock methadone because of its association with the treatment of heroin addiction (Toombs and Kral, 2005).

In November 2006, the Food and Drug Administration (FDA) issued a warning regarding careful prescribing of methadone because of the marked rise in overdose deaths among patients receiving methadone for pain, and it revised the interval for recommended starting dosage (from 2.5–10 mg every 3–4 hours to 2.5–10 mg every 8–12 hours). In January 2008, methadone manufacturers voluntarily limited distribution of the largest (40 mg) formulation of methadone to authorized opioid addiction treatment programs and hospitals only, because this formulation was not approved for the treatment of pain (CDC, 2012). Oral (tablet and liquid) and injectable methadone formulations are available in the US, as is methadone powder for compounding.

Data suggest that some of the current uses of methadone for pain in the US might be inappropriate (CDC, 2012). Previously reported indications for methadone were musculoskeletal problems (46%), headaches (17%), cancer (11%), and trauma (5%) (Governale, 2010). Most methadone prescriptions were written by primary care providers or mid-level practitioners rather than pain specialists, and nearly one third of prescriptions appear to have been dispensed to opioid-naïve patients (Governale,

2010).This has prompted the CDC to state that methadone should not be indicated as a first-line strategy for chronic pain. Rather, it should be reserved for pain-related conditions for which the benefits likely outweigh the risks to patients and society, such as use for cancer-related pain or palliative care (CDC, 2012).

To address safety concerns for the use of methadone for maintenance therapy and chronic non-cancer pain, the American Pain Society released guidelines in 2014 entitled, *Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society*. The guidelines provide recommendations developed by a multidisciplinary expert panel, however, the panel acknowledges that most recommendations were based on low-quality evidence, and no recommendations were based on high-quality evidence (Chou et al., 2014). These guidelines come two years after the publication of the American Society of Interventional Pain Physicians guidelines entitled, *American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2-guidance*.

KEY REFERENCES: Methadone use in select developed countries
(*See Excel Sheet 1 for more references)*

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CHAPTER 3: METHADONE AND CANCER PAIN

This chapter provides recent evidence that supports the use of methadone as an alternate opioid for managing pain in cancer patients. A growing body of evidence supports the use of methadone for controlling bone pain, breakthrough pain, incident pain, and neuropathic pain in cancer patients. However, few randomly controlled clinical trials examining the benefits of methadone for analgesia exist, and recommendations for methadone in treating cancer pain often conflict. In the 2014 National Comprehensive Cancer Network (NCCN) guidelines entitled *NCCN Guidelines Version 2.2014 Adult Cancer Pain,* methadone is recommended but this recommendation is based on lower level evidence (NCCN, 2014). The guidelines contain "Special notes regarding oral methadone" advising practitioners to consult with a pain or palliative care specialist on rotation and titration of methadone if they are unfamiliar with prescribing methadone, or if an individual patient's interests require very rapid switching to or from methadone (NCCN, 2014). In contrast, methadone is excluded from the 2014 NCCN guidelines for palliative care entitled, *NCCN Guidelines Version 1.2014 Palliative Care* (NCCN, 2014). Continuing medical education that focuses on opioid prescription is crucial to cancer pain management (Gallagher et al., 2004).

In the European Society for Medical Oncology (ESMO) *Management of Cancer Pain: ESMO Clinical Practice Guidelines,* morphine is recommended as the first line strong opioid. The ESMO concedes that methadone is a valid alternative to morphine; however, because of marked interindividual differences in its plasma half-life and duration of action, it is still considered as a drug which should be initiated by physicians with experience and expertise in its use (Ripamonti et al., 2012).

Approximately 80% of cancer patients experience moderate to severe pain in the advanced stages of illness, and a subset of these patients are unresponsive to morphine or develop dose-limiting toxicities as morphine doses are escalated (Davies et al., 2001). Under these circumstances, methadone may be considered as an alternate and highly potent mu agonist that acts as both a short-term and long-term analgesic and that displays an analgesic efficacy similar to that of morphine (Davies et al., 2001; Nicholson, 2007). It is important to note that cancer pain may be caused by multiple different mechanisms. Therefore, therapy should address those underlying mechanisms and not simply be based on pain intensity, as recommended by the WHO analgesic ladder (Müller-Schwefe et al., 2014). In Canada, a recent survey of cancer patients from four Canadian centers indicates that breakthrough cancer pain greatly negates daily activity, and only 35% of cancer patients are very satisfied with the speed of relief of their pain medications (Bédard et al., 2013).

Recent recommendations and findings for methadone use in treating cancer pain:

- The European Palliative Care Research Collaborative (EPCRC) and the European Association for Palliative Care (EAPC) provide a weak recommendation for methadone as a step 3 opioid of first or later choice for moderate to severe cancer pain; yet, it is better reserved for more skilled professionals (Caraceni et al., 2011; Caraceni et al., 2012)
- Methadone for analgesia is a safe and useful alternative to morphine; it may control cancer pain that is difficult to manage with other opioids (Ripamonti, 2012)

- Outpatient initiation of methadone and rotation for cancer pain is safe, exhibits high success rates, and has a low side effect profile (Parsons et al., 2010)
- For breast cancer patients with bone metastases, methadone should be restricted to patients with difficult pain syndromes (Schneider et al., 2012)
- Methadone may be used as an additional opioid for a cancer patient with severe neuropathic and bone pain not responsive to other opioids (Leppert and Kowalski, 2013)
- Addition of methadone to another opioid treatment regimen can efficiently manage moderate to severe cancer pain (Wallace et al., 2013)
- Intravenous patient-controlled methadone may provide timely, safe, and useful analgesia for patients with severe breakthrough cancer pain; further, it may be useful to help titration of opioids and weaning to oral analgesia (Sousa et al., 2014)
- The EPCRC guideline group provides a weak recommendation that methadone be used for step 3 combined opioid therapy for cancer pain (morphine plus oxycodone or fentanyl/methadone) (Fallon and Laird, 2011)
- The addition of fentanyl buccal tablets is effective in controlling breakthrough pain for cancer patients already receiving methadone for background analgesia (Mercadante et al., 2011)
- The conversion ratio from oral morphine to oral methadone is affected by previous opioid use and varies widely from 1:5 to 1:12 or more (Mercadante and Caraceni, 2011; Caraceni et al., 2012)

- Best practice for terminally ill patients with cancer pain should include monitoring of pain and plasma methadone concentration (Auret et al., 2006)
- Methadone may achieve pain relief for patients with phantom limb pain but controlled randomized trials are needed to verify this observation (Bergmans et al., 2002)
- Oral methadone improved pain in a patient with tenesmus associated with locally advanced rectal carcinoma (Mercadante et al., 2001)

KEY REFERENCES: METHADONE AND CANCER PAIN

(See Excel Sheet 1 for more references)

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CHAPTER 4: METHADONE AND CHRONIC NON-CANCER PAIN

If treatment of chronic non-cancer pain with non-opioid and adjunctive analgesics fails to decrease pain and improve function, opioids may be indicated (Gourlay et al., 2005). The use of methadone for chronic non-cancer pain is described in the Canadian NOUGG guidelines entitled, *Canadian guideline for safe and effective use of opioids for chronic non-cancer pain*. These guidelines are divided into five broad topics: 1) Deciding to initiate opioid therapy; 2) Conducting an Opioid Trial; 3) Monitoring long-term opioid therapy (LTOT); 4) Treating Specific Populations with LTOT; 5) Managing Opioid Misuse and Addiction in chronic non-cancer pain patients. (NOUGG guidelines for chronic-non-cancer pain are provided in PDF format as part of the *Methadone for analgesia*: state assessment). Other prescribed use of methadone for non-cancer pain has been reported for end stage renal disease, perioperative pain, and sickle cell disease.

Despite limited evidence and variable development methods, internationally recognized guidelines for opioids in chronic non-cancer pain concede that recommendations should comprise management strategies that describe upper dosing thresholds, possible drug–drug interactions; risk assessment tools, treatment agreements, and urine drug testing (Manchikanti et al, 2012; Nuckols et al., 2014).

Recent recommendations and findings for methadone use in treating non-cancer pain:

- NOUGG recommends methadone as a third-line strategy for severe non-cancer pain (Kahan et al., 2011)

- The American Society of Interventional Pain Physicians guidelines recommend methadone for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses (Manchikanti et al., 2012)
- When considering initiation of methadone, the American Pain Society recommends that clinicians perform an individualized medical and behavioural risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (Chou et al., 2014)
- Patient-controlled analgesia with methadone prompts less opioid consumption and lower pain scores at rest and at motion in comparison with morphine as postoperative analgesia after hip surgery (Neto et al., 2014)
- Fentanyl and methadone are considered the safest opioids for symptom management in patients with end-stage renal disease (O'Connor and Corcoran, 2012)
- For adult patients with sickle cell disease, there are no differences in pain or affective response in patients treated with methadone or morphine or oxycontin (Feliu et al., 2011)
- Methadone may be considered for pain associated with herpes zoster and post-herpetic neuralgia (Gan et al., 2013)

KEY REFRENCES: METHADONE AND CHRONIC NON-CANCER PAIN
(See Excel Sheet 1 for more references)

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CHAPTER 5: METHADONE DELIVERY AND FORMULARY AVAILABILITY

This chapter reports on different methadone delivery modes and formulations. In addition, an overview of global formulary availability is provided.

Methadone is primarily administered orally via tablet or liquid formulation. It is parenterally administered via continuous and/or intermittent bolus infusion with a Mediport, peripheral intravenous (IV) line, a peripherally inserted central catheter, a midline catheter, and a subcutaneous line (Shaiova et al., 2008). Additional methadone delivery modes include epidural, intrathecal, rectal, subcutaneous, sublingual, and topical administration. In Canada, methadone is available in oral tablet or liquid formulation (tablet [1, 5, 10 and 25 mg strengths], oral suspension [1–10mg/ml; also available in dye-free/sugar-free/unflavoured solution]). Further, methadone powder is available for compounding. Marketed methadone formulations approved by Health Canada are listed in Table 5.1. However, formulary availability differs between provinces. Injectable methadone may be procured through Health Canada via the Special Access Program. In addition, several independently created syringe driver prescription charts and protocols are available at Palliativedrugs.com to guide healthcare providers through administration of IV methadone (www.palliativedrugs.com).

Table 5.1 Marketed methadone formulary approved by Health Canada as of July 2014 (modified from Health Canada, 2014)

Brand	**Drug**	**DIN**	**Company**	**Formulation**	**Concentration**
Cophylac drops	Normethadone hydrochloride	02224577	Valeo Pharma Inc.	Oral; liquid	10 mg/ml
Metadol	Methadone hydrochloride	02241377	Paladin Labs Inc.	Oral; liquid	10 mg/ml
Metadol	Methadone hydrochloride	02247694	Paladin Labs Inc.	Oral; liquid	1 mg/ml
Metadol	Methadone hydrochloride	02247698	Paladin Labs Inc.	Oral; tablet	1 mg
Metadol	Methadone hydrochloride	02247699	Paladin Labs Inc.	Oral; tablet	5 mg
Metadol	Methadone hydrochloride	02247700	Paladin Labs Inc.	Oral; tablet	10 mg
Metadol	Methadone hydrochloride	02247701	Paladin Labs Inc.	Oral; tablet	25 mg
Metadol-D	Methadone hydrochloride	02244290	Paladin Labs Inc.	Oral; liquid	10 mg/ml
Methadose	Methadone hydrochloride	02394596	Mallinckrodt Canada Ulc.	Oral; liquid	10 mg/ml
Methadose	Methadone hydrochloride	02394618	Mallinckrodt Canada Ulc.	Oral; liquid	10 mg/ml

- Optimal pain management with solid, oral formulations is challenging for patients with chronic pain, including pediatric, geriatric, and palliative care patients, who suffer from dysphagia (Pergolizzi et al., 2014)
- Parenteral administration is often necessary in end-of-life care when patients are no longer able to take oral medication (Destro et al., 2012)

- Sublingual administration of methadone may be advantageous because of rapid analgesic onset and avoidance of hepatic first-pass metabolism (Reisfield and Watson, 2007); it provides relief for breakthrough cancer pain (Hagen et al., 2010), and has been successfully administered to a patient with chemotherapy- and radiation-induced mucositis (Gupta et al., 2010)

- Altering tablets by cutting, crushing, or grinding medication to facilitate swallowing could alter drug pharmacokinetics and lead to serious adverse events (Pergolizzi et al., 2014)
- Topically applied methadone has been administered successfully for patients with chronic non-cancer pain and cancer pain. The oral dose q8h and prn (often reduced by 30%) may be compounded by an experienced pharmacist with Lipoderm ® (10 mg/0.2 ml =5% methadone powder 2.65 g, ethoxy diglycol 4.20 ml and Lipoderm® 47 g cream). Concentration range was 2 mg/0.2 ml to 25 mg/0.2 ml (Love and Bourgeois, 2014)
- Topical methadone powder (100 mg mixed in 10 g Stomahesive powder and sprinkled on an open wound once daily at the time of dressing change) is effective for pain relief in open, exudative wounds with little eschar (Gallagher et al., 2005); however, topical application of methadone powder (10-45 mg/day dissolved in ethoxydiglycol added to the calculated volume of pluronic lecithin organogel) does not result in trough methadone serum concentrations associated with analgesia (Sylvester et al., 2011)
- Continuous subcutaneous methadone infusions may produce local intolerance; intermittent subcutaneous intermittent methadone infusion is a useful alternative

to oral administration in selected clinical situations when oral administration is not feasible (Centano and Vara, 2005)

- Epidural methadone plus lidocaine effects dose-dependent analgesia that is improved by epidural dexamethasone (Lauretti et al., 2013)
- Rectal administration of methadone results in rapid absorption, a high bioavailability and long duration of action of approximately 10 h (Dale et al., 2004); methadone suppositories may be extemporaneously prepared (MD Anderson Cancer Center, 2005)
- Intrathecal methadone infusion has been considered for intractable cancer pain in tertiary palliative care centers (Hawley et al., 2009)

Global methadone formulary availability and regulations

Oral methadone (liquid and tablet form) is priced lower than several morphine formulations in most countries when available; it is most consumed in China, Iran, New Zealand, Tanzania, and the UK (De Lima et al., 2014). A report on availability and accessibility of opioids for the management of cancer pain in Europe was published in 2010 by the Global Opioid Policy Initiative (GOPI) project (Cherny et al., 2010). In 2013, the GOPI published a report on availability and accessibility of opioids for the management of cancer pain in Africa, Asia, Latin America and the Caribbean, as well as the Middle East.

- In Africa, palliative care for cancer patients is inconsistent. Access to simple pain-relieving medication is limited and opioids are legally restricted. Other limiting factors include deficiencies in the supply chain, a lack of pharmacists in public

health services, and widespread restriction of prescriptive authority (Cleary et al., 2013). Most African countries surveyed (15/25) have restrictive laws for opioid prescription, with special prescription forms needed (16/ 25); in four countries, physicians must pay for these forms. Prescription limits range from 2 days–30 days. Oral methadone for cancer pain is only available in two African countries: Mauritius (free), and occasionally available in Liberia at full cost (Cleary et al., 2013a)

- In Asia, opioid consumption has not increased at the same rate as global opioid consumption. Formulary deficiencies are severe in several countries, are often unavailable, and access is significantly impaired by widespread over-regulation. All physicians are permitted to prescribe opioids in Afghanistan, Bhutan, Cambodia, China-Hong Kong, Indonesia, Japan, Korea, Malaysia, Nepal, Sri Lanka and Thailand. Remaining surveyed countries require special authorization. In addition, approximately half of the surveyed countries had restrictions on prescription forms, and for some of these, physicians must pay for these forms. Prescription limits ranged form 5 days–60 days. Oral methadone is available in seven countries: China and China-Hong Kong (usually available and < 25% cost); Malaysia (available half the time and at < 25% cost); Phillipines (available half the time and at full cost); Thailand (occasionally available and free); and Vietnam (occasionally available and free) (Cleary et al., 2013b)
- In Europe, many patients do not receive adequate relief of pain because of regulations that restrict opioid availability and accessibility. Most of the East-European and a minority of the West-European countries require that patients,

particularly outpatients, receive a permit or be registered to be eligible to receive opioid prescriptions for the management of cancer pain. In some European countries, this also applies to hospice patients. Some countries restrict the authority to prescribe opioids to physicians with special permits or to practitioners of certain subspecialties. All East-European countries and most of West-European countries require that opioids be prescribed using duplicate or triplicate prescriptions. Some countries report that access to forms is difficult, and in some countries physicians must pay for these forms. Prescription limits range from 1 day at a time to no limits. In Western Europe, methadone for cancer pain is available at varied cost in most countries (17/21 surveyed countries). Exceptions include: Cyprus, Greece, Portugal, and Turkey. In Eastern Europe, methadone is available in 10 of 22 surveyed countries (Cherny et al., 2010)

- In India, opioid consumption has not increased at the same rate as global opioid consumption. When opioids are on formulary, they are often unavailable and access is significantly impaired by widespread over-regulation that continues to be pervasive across the nation. In most survey states, primary care physicians require special authorization to prescribe opioids, and in four states (Bihar, Haryana, Punjab and Tamil Nadu), they can only prescribe opioids in emergency situations. More than 50% of surveyed states and regions (15/25) require duplicate or triplicate prescription forms; they are free everywhere except Kerala. Prescription limits range from 3 days–30 days. Importantly, methadone is not available in any Indian state (Cleary et al., 2013c)

- In Latin America and the Caribbean, palliative care is at varied stages of development and opioid consumption is variable. In 18 of 24 surveyed countries, oncologists are always allowed to prescribe opioids while family physicians require special authority in two surveyed countries. Almost all surveyed countries require special prescription forms that are generally readily available, but at a cost to the physician. Prescription limits range from 3 days–30 days. Oral methadone is primarily available in Central America and the Caribbean (15 of 24 surveyed countries) (Cleary et al., 2013d)
- In the Middle East, there is little increase in opioid consumption when compared with global consumption. Formulary deficiencies are severe in several countries in particular Afghanistan, Iraq, Lebanon, Libya, Palestine, and Tunisia. When opioids are on formulary, they are often unavailable, and access is significantly impaired by widespread over-regulation that is pervasive across the region (Cleary et al., 2013e). In Afghanistan, Israel and Morocco, all physicians are permitted to prescribe opioids but special authorization was required in most countries for both surgeons and family physicians. Special prescription forms are required, yet access to these prescription forms is restricted. In three surveyed Middle Eastern countries, physicians must pay for these forms. Prescription limits range from 3 days–30 days. Oral methadone is always available in Quatar (full cost), usually available in Iran, Israel, and Morocco (full cost), and occasionally available in Afghanistan (full cost) (Cleary et al., 2013e)

KEY REFERENCES: METHADONE DELIVERY AND FORMULARY

(See Excel Sheet 1 for more references)

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CHAPTER 6: METHADONE CONVERSION, ROTATION, AND SWITCHING

Methadone conversion, rotation and switching are complicated and equianalgesic opioid doses are difficult to predict. This chapter describes the common challenges encountered when converting from other opioids to methadone.

Safe conversion or rotation to methadone is best practiced with close monitoring to ensure adequate analgesia and minimal side effects (Shaiova et al., 2008). The conversion table outlined in the NOUGG guidelines for chronic non-cancer pain is provided in Table 6.1. For adult cancer pain, a conversion table for oral morphine to oral methadone is available in the *NCCN Guidelines Version 2.2014 Adult Cancer Pain* (copyright protected). However, the dose ratio of morphine to methadone is neither constant nor predictable. Switching back from methadone to another opioid may be even more challenging. As such, physicians who are not well acquainted with switching patients to methadone should consult a palliative care specialist. Moreover, a customized and cautious approach is advisable when rotating to oral methadone, especially in patients who have experienced opioid toxicity (Kilonzo and Twomey, 2013). To further facilitate this process, several examples of methadone titration charts and conversion tables created by independent palliative care hospices are shared on Palliativedrugs.com (Pilgrims Hospices, 2005; Highlands Hospice, 2010; Western Sydney Health Area Health Service, 2010).

Table 6.1 NOUGG opioid conversion table for patients with chronic non-cancer pain (Kahan et al., 2011)

Table 4. Oral opioid analgesic conversion table based on oral dosing for chronic noncancer pain: *A) Equivalence to 30 mg of oral morphine; B) Equivalence between oral morphine and transdermal fentanyl.*

A)

OPIOID	EQUIVALENCE TO 30 MG ORAL MORPHINE	TO CONVERT TO ORAL MORPHINE EQUIVALENT MULTIPLY BY ...	TO CONVERT FROM ORAL MORPHINE MULTIPLY BY ...
Morphine	30 mg	1	1
Codeine	200 mg	0.15	6.67
Oxycodone	20 mg	1.5	0.667
Hydromorphone	6 mg	5	0.2
Meperidine	300 mg	0.1	10
Methadone and tramadol	Morphine dose equivalence not reliably established		

B) TRANSDERMAL FENTANYL*	MORPHINE
25 µg/h	60-134 mg
37 µg/h	135-179 mg
50 µg/h	180-224 mg
62 µg/h	225-269 mg
75 µg/h	270-314 mg
87 µg/h	315-359 mg
100 µg/h	360-404 mg

*Formulations include 12-, 25-, 50-, 75-, and 100-µg/h patches, but the 12-µg/h patch is generally used for dose adjustment rather than initiation of fentanyl treatment.
Adapted from the National Opioid Use Guideline Group.[5] Data from the *Compendium of Pharmaceutical and Specialties*[27] and Pereira et al.[49]
Wide ranges have been reported in the literature. These equivalences refer to analgesic strength of oral opioids and not psychoactive effects or effectiveness in relieving withdrawal symptoms.

Many methadone switching methods have been described. These include, but are not restricted to, the Edmonton method, the German method, and the Morley-Makin method.

- The Edmonton method relies on using a 10:1 morphine to methadone equianalgesic dose conversion and then converting gradually over three days. This is achieved by reducing the previous opioid dose by increments of 1/3 of the initial dose daily, and introducing methadone in increments of 1/3. Methadone is

prescribed on a q8 hourly basis (Dian and Hawley; on behalf of the CPSBC, 2010)

- The German model relies on a rapid switchover to levamethadone and it is designed for patients taking more than 600 mg oral methadone per day. The pre-existing opioid is stopped, then titration of oral levamethadone is initiated with a starting dose of 5 mg orally q 4 h (plus prn q 1 h). If necessary, the levamethadone dose may be increased (pain) or decreased (side effects) by 30% q 4 h (plus prn q 1 h). After 72 h, the achieved single dose is maintained, but the dosing interval increases two-fold to q 8 h (plus prn q 3 h) (Ostgathe et al., 2012) This approach has proven practical and safe approach for opioid rotation to levamethadone in a retrospective analysis of 52 patients in a palliative care setting (Ostgathe et al., 2012)
- The Morley-Makin method relies on patient-controlled analgesia; for the first few days the dosing is only on a prn basis until the optimal dose is found (Morley et al., 2003)
- The traditional ratio for methadone conversion from the oral route to the parenteral route may produce toxicity problems; a modified conversion ratio of 0.7 (oral: parental = 1:0.7) is recommended as it approximates the bioavailability of the drug administered orally (González-Barboteo et al., 2008)
- Opioid rotation from methadone to another opioid may be complicated by worsening pain and dysphoria (Moryl et al., 2002)

Methadone dosage

It is important to note that dosage and rapid titration methods use for other opioids do not apply to methadone.

- Methadone dosages should not be increased more frequently than every 3 to 4 days except under close supervision (Dian and Hawley; on behalf of the CPSBC, 2010)
- Methadone is not effective for chronic pain as a single daily dose and it is usually prescribed as one dose every 8 h (Dian and Hawley; on behalf of the CPSBC, 2010)
- Once patients are on a stable methadone dose, the dose should be adjusted by increments of 10%–20% and no more frequently than every 3 days. For elderly patients or patients with impaired liver function, this adjustment period should be increased (Dian and Hawley; on behalf of the CPSBC, 2010)
- Breakthrough methadone doses are between 5%–20% of the total daily dose. For breakthrough cancer pain, a short-acting opioid such as morphine, hydromorphone or oxycodone should be provided during the conversion and dose-titration periods. Use of methadone for breakthrough pain should be avoided in the titration phase. Once a patient is stable on a regular dose of methadone, a short-acting opioid should be used incident pain to avoid accumulation and inadvertent methadone overdose. If using methadone for breakthrough pain, it is prudent to limit daily prn doses to 3 doses per day to avoid accumulation (Dian and Hawley; on behalf of the CPSBC, 2010)

KEY REFERENCES: METHADONE CONVERSION, ROTATION, AND SWITCHING
(See Excel Sheet 1 for more references)

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CHAPTER 7: METHADONE SAFETY

Safe use of methadone use for analgesia can reduce the risk of life-threatening toxicity and adverse effects. This chapter discusses the risk factors for methadone toxicity and mortality, commonly reported adverse effects, and major pharmaceutical groups associated with possibly harmful drug-drug interactions.

Opioid toxicity

Opioid toxicity results from build-up of toxic metabolites and it is characterized by any combination of manifestations listed in Table 7.1 (Taube, 2003). While the effects of overdosing are seen within 8–12 hours for morphine, hydromorphone and oxycodone, a methadone overdose may manifest only after many hours, or possibly up to 3 or 4 days later. A patient who has had many breakthroughs in a 24 h period (more than 5) or who had their methadone doses increased rapidly over a short period of time should be monitored closely for at least 3 to 4 days after the last dose increase. Being able to differentiate between features of serious opioid toxicity and features of advanced progressive disease is equally important (Saint Francis Hospice, 2007).

Table 7.1 Manifestations of opioid toxicity (Taube, 2003)

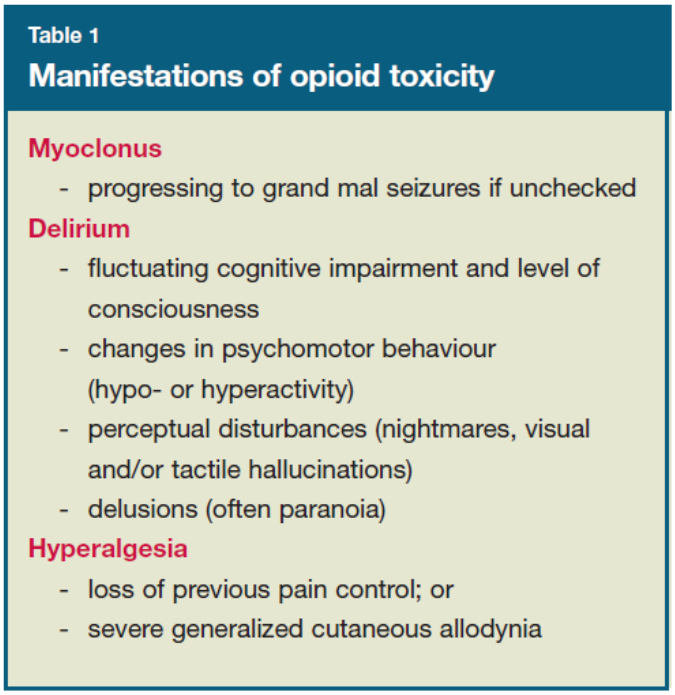

Table 1

Manifestations of opioid toxicity

Myoclonus
- progressing to grand mal seizures if unchecked

Delirium
- fluctuating cognitive impairment and level of consciousness
- changes in psychomotor behaviour (hypo- or hyperactivity)
- perceptual disturbances (nightmares, visual and/or tactile hallucinations)
- delusions (often paranoia)

Hyperalgesia
- loss of previous pain control; or
- severe generalized cutaneous allodynia

- Opioid overdoses, including excessive sedation and respiratory depression, typically occur with excessively rapid dose escalations during the initial titration phase, prior to reaching steady state (Shaiova et al., 2008)
- Methadone contributes disproportionately to the excessive number of opioid pain reliever overdoses and associated medical/societal costs in the US (CDC, 2012). Medical examiner data suggest more than three quarters of methadone overdoses involve persons who were not enrolled in methadone maintenance programs and that most persons who overdosed were using it without a prescription. Between 1999 and 2009, however, the rate of fatal overdoses involving methadone increased more than fivefold as its prescribed use for treatment of pain increased (US Government Accountability Office; 2009; US Department of Health and

Human Services, Substance Abuse and Mental Health Services Administration; 2010) Thus, health-care providers who choose to prescribe methadone should have substantial experience with its use and follow consensus guidelines for appropriate opioid prescribing (CDC, 2012)

- In Ontario, Canada, methadone had the highest relative percentage of deaths which were accidental (84%) when compared with other opioids (Madadi et al., 2013)
- Administration of the opioid reversal agent naloxone is effective in treating opioid toxicity resulting from licit, in-hospital methadone use (Neil et al., 2013)
- Naltrexone can substitute for naloxone and is efficient in the prevention of recurrent or delayed respiratory arrest in opioid-naive methadone-intoxicated patients; it shortens hospitalization duration and decreases the risk of complications (Aghabiklooei et al., 2013)
- Opioid toxicity may be managed with opioid rotation (decrease the new opioid equianalgesic dose by approximately 25%), hydration (~1.5-2.0 L/24 h), and short-term antipsychotic use, if clinically indicated (haloperidol 1 mg orally/subcutaneously every hour as needed) (Taube, 2003)

KEY REFERENCES: METHADONE SAFETY
(See Excel Sheet 1 for more references)

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Methadone adverse effects

The most frequently observed adverse reactions to methadone include adverse cardiac outcomes, constipation, diaphoresis, dizziness, and lightheadedness. As with other opioids, nausea and mild sedation may occur upon initiation of treatment but these usually resolve spontaneously after 3 to 5 days. Methadone, however, is less constipating than other opioids (Mancini et al., 2000). Other reported side effects for methadone include edema, hyperalgesia, hypoglycaemia, hypogonadism, myoclonus, respiratory depression, serotonin syndrome, and sleep apnea. These side effects are usually dose-dependent and may be avoided, or treated if monitored carefully (Shiaova et al., 2008). Side effects are often more prominent when therapy is initiated; once a patient is on a stable opiate analgesic dose, side effects are less bothersome (Shaiova et al., 2008).

Methadone and adverse cardiac outcomes

Evidence suggests that methadone can prolong QTc intervals and may induce torsades de pointes (TdP). A QTc interval, detected with an electrocardiogram (ECG), ≥ 500 milliseconds (ms) is associated with an increased risk for TdP (Roden, 2002; Huh and Park, 2010).

- An electrocardiogram (ECG) should be obtained prior to initiation, at 30 days and yearly thereafter for methadone prescription (Manchikanti et al., 2012)
- IV methadone has a significantly greater risk of QT prolongation than oral methadone (Shaiova et al., 2008)
- A prospective study of 100 palliative care patients receiving methadone for pain at a median dose of 23 mg per day reported 31% of patients had QTc prolongation at two weeks of therapy and 11% of patients had QTc prolongation at eight weeks of therapy (Reddy et al., 2010)
- A retrospective study of over 500 patients found no patients with a QTc interval > 500 ms with a median methadone dose of 30 mg per day; however, only 11% of the patients had ECG monitoring within three months before and after starting methadone (Reddy e t al., 2004)
- Healthcare providers are encouraged to inform patients of methadone's arrhythmia risk; review patient history for structural heart disease, arrhythmias, and syncope; obtain an ECG before and 30 days after starting therapy, then annually; discuss the risks and benefits of therapy if the patient's QTc is > 450 ms but < 500 ms; and be aware of the concomitant use of potentially interacting or other QTc prolonging medications; healthcare providers should further consider

decreasing the dose or discontinuing therapy if the QTc is >500 ms and obtain an ECG when methadone doses are >100 mg/day or when clinically indicated (Krantz et al., 2009)

- In a retrospective study of 1246 patients treated with methadone for chronic and non-chronic pain, few cardiac adverse events from methadone use for pain were detected; however, a large proportion of patients were at risk for an adverse event, especially patients who were older and had received > 100 mg methadone per day (Price et al., 2014)
- The American Pain Society recommends that clinicians obtain an ECG prior to initiation of methadone in patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc > 450 ms, or a history suggestive of prior ventricular arrhythmia; An ECG within the past three months with a QTc < 450 ms in patients without new risk factors for QTc interval prolongation can be used for the baseline study (Chou et al., 2014)
- Some drugs and medical conditions may prolong QTc (described below in Methadone drug-drug interactions). Medical conditions considered risk factors for QTc prolongation include electrolyte abnormalities such as hypokalemia or hypomagnesemia, impaired liver function, structural heart disease (such as congenital heart defects or a history of endocarditis or heart failure) and genetic predisposition such as congenital prolonged QT syndrome or familial history of prolonged QT syndrome (Chou et al., 2014)

- Mutations in *KCNH2*, the gene that encodes the cardiac potassium voltage-gated channel hERG, may also contribute to QTc prolongation in patients receiving methadone (Hajj et al., 2014)

KEY REFERENCES: Methadone adverse effects
(See Excel Sheet 1 for more references)

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Methadone and edema

Several case reports describe pulmonary edema in patients taking methadone maintenance therapy (MMT) (Mahé et al., 2004). Peripheral and pulmonary edema has been reported in patients prescribed methadone for analgesia.

- Peripheral edema observed in patients taking methadone for chronic back pain (Kharlamb and Kourlas, 2007; Dawson et al., 2014)

KEY REFERENCES: Methadone and edema

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Methadone and myoclonus

Myoclonus is an involuntary shock-like contraction, irregular in rhythm and amplitude, followed by relaxation, of a muscle or a group of muscles. Myoclonus is associated with high-dose parenteral methadone in patients with cancer under hospice care (Sarhill et al., 2001; Ito and Liao, 2008).

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Methadone and respiratory depression

Opioids induce respiratory depression via activation of mu opioid receptors at specific sites in the central nervous system; opioid-induced respiratory depression can be fatal but may be reversed with naloxone (Boom et al., 2012, NCCN, 2014).

- Methadone accumulation can lead to sedation, respiratory depression, respiratory arrest, and death in opioid-naïve and opioid-tolerant patients (Modesto-Lowe et al., 2010)
- Individual differences in the ability to metabolize methadone, along with imperfect cross-tolerance, may heighten risks of respiratory depression during the methadone induction period (Modesto-Lowe et al., 2010)
- The peak respiratory depressant effect of methadone appears later and persists longer than its analgesic effect, especially early in treatment (Modesto-Lowe, 2010)
- Prior to 2000, reports of opioid-induced respiratory depression involved use of morphine in cancer pain; since 2000, reports of opioid-induced respiratory depression predominantly involve methadone or transdermal fentanyl in non-cancer pain patients (Dahan et al., 2013)
- Hospitalized patients on general medical units taking opioids for analgesia that required naloxone to reverse opioid-induced oversedation or respiratory depression had significantly more risk factors (e.g. comorbid renal disease, cardiac disease, respiratory disease, concurrent use of central nervous system-sedating medication, and smoking) than matched patients who did not require naloxone (Pawasauskas et al., 2014)

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Methadone and serotonin syndrome

Serotonin syndrome results from excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors. It is often described as a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (Bush et al., 2006).

- Serotonin syndrome reported in a chronic pain patient receiving concurrent methadone, ciprofloxacin, and venlafaxine (Lee et al., 2009)
- Serotonin syndrome reported in a palliative care patient taking methadone (Bush et al., 2006)

KEY REFERENCES: Methadone and serotonin syndrome

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Methadone and sleep apnea

Central sleep apnea is associated with chronic opioid use and MMT. In addition, abnormal sleep architecture (reduction of rapid eye movement and slow wave sleep) has been reported during opioid induction and withdrawal (Wang and Teichtahl, 2007).

- There is a direct relationship between the apnea-hypopnea index and daily dosage of methadone in chronic pain patients (Webster et al., 2008)
- Severe central sleep apnea reported in a pediatric cancer patient on chronic methadone therapy (Amos and D'Andrea, 2013)

KEY REFERENCES: Methadone and sleep apnea

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Methadone and hyperalgesia

Opioid-induced hyperalgesia is a response to opioid agonists resulting in increased sensitivity to pain (Ramasubbu and Gupata, 2011).

- Methadone for cancer pain, non-cancer and chronic pain may contribute to an increase in sensitivity to certain experimental pain stimuli (Hay et al., 2009; Kaye et al., 2014)
- Methadone successfully treated opioid-induced hyperalgesia in a cancer patient treated for several years with high doses of other opioids (Axelrod and Reville, 2007)

- Use of very-low-dose methadone in conjunction with adjuvant haloperidol controls pain without dose escalation or opioid-induced hyperalgesia in both cancer and non-cancer patients (Salpeter et al., 2013)

KEY REFERENCES: Methadone and hyperalgesia

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Methadone and hypoglycaemia

Symptomatic hypoglycaemia (unexplained sweating, palpitations, or lethargy) during methadone titration has been mistaken for methadone overdose.

- Rapid methadone dose escalation in opioid-tolerant patients with cancer is associated with hypoglycaemia (Moryl et al., 2013)

KEY REFERENCE: Methadone and hypoglycaemia

Moryl N, Pope J, Obbens E. Hypoglycemia during rapid methadone dose escalation. J Opioid Manag. 2013; 9(1): 29-34.

Methadone and hypogonadism

Hypogonadism may occur in patients taking opioids for cancer pain (McWilliams, et al., 2014) and non-cancer pain (Daniell et al., 2006).

- Dose-related dehydroepandrosterone dehydroepiandrosterone sulphate deficiency is found in a majority of non-hospitalized adults who are chronically consuming sustained-action oral or transdermal opioids for non-cancer pain (Daniell, 2006)
- Men with advanced pancreatic cancer that take opioids have reduced luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. Further, there is an association between opioid use and reduced LH/FSH levels in postmenopausal women with pancreatic cancer (Skipworth, 2011)
- Hypogonadism in advanced cancer patients (men and women) is associated with poorer survival (Skipworth et al., 2011)

KEY REFERENCES: Methadone and hypogonadism

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Methadone and drug-drug interactions

Many drug-drug interactions for methadone have been reported with cytochrome P450, family 3, subfamily A (CYP3A) inhibitors, CYP3A inducers, and antiviral medications. Importantly, many dugs are associated with QTc prolongation (Table 7.2). Prescribers of methadone and pharmacists should enquire about any new medications periodically, and particularly when a stable patient suddenly experiences drug craving, withdrawal, or intoxication (Kapur et al., 2011).

- CYP3A inhibitors (e.g. fluconazole, voriconazole, ciprofloxacin, erythromycin, and grapefruit juice) reduce methadone clearance and could cause toxicity (Overholser and Foster, 2011)
- CYP3A inducers (e.g. rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort) may induce methadone metabolism of methadone and reduce methadone exposure, possibly causing opioid withdrawal (Overholser and Foster, 2011)
- Cytochrome P450, family 2, subfamily B, polypeptide 6 (CYP2B6) inhibitors may decrease methadone metabolism and increase opioid effects while CYP2B6 inducers induce methadone metabolism and decrease its effects (Overholser and Foster, 2011)
- Non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) induce CYP3A and can increase methadone requirements and/or induce opioid withdrawal (Ferrari et al., 2004); protease inhibitors (e.g. darunavir/ritonavir, lopinavir/ritonavir, nelfinavir, and tipranavir/ritonavir) may reduce methadone concentrations and may cause opioid withdrawal; selective serotonin reuptake inhibitors (e.g. sertraline, paroxetine, and fluvoxamine) inhibit cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) and can increase methadone plasma concentrations, resulting in increased opioid effects or toxicity (Overholser and Foster., 2011)
- St John's wort decreases plasma concentrations of methadone (Zhou et al., 2004)

- Co-administration of lofexidine and methadone may induce QTc prolongation; this drug combination should be prescribed cautiously, with ECG monitoring (Schmittner et al., 2009)
- Ventricular bigeminy with concomitant administration of methadone, voriconazole and esomeprazole was reported in a Caucasian woman aged 26 with acute lymphoblastic leukaemia (Scholler et al., 2011)
- Several drugs have QTc-prolonging properties: antidepressants (amitriptyline and imipramine), antipsychotics (haloperidol), antibiotics (erythromycin), antimalarials (chloroquine), and antiarrhythmics (Chou et al., 2014)

Table 7.2 Methadone interactions and effect on methadone half-life (Kapur et al., 2011)

Table 1. Methadone: Drug-drug interaction and impact on methadone half-life.

Drug	T½ Methadone	Comments	References
Abacavir	Decrease	5 patients had a net 35% decrease of methadone plasma levels after administration of abacavir and methadone. Abacavir increases methadone clearance, leading to a decrease in methadone half life. Interaction is not likely clinically relevant.	(12,65,66)
Age	Variable	No significant change in AGP concentrations was detected among patients between the ages of 20–90 years. Methadone clearance tends to be low in the elderly. Elderly patients were found to be sensitive to low doses of methadone.	(201–206)
Alcohol	No effect	Acute drinking of alcohol showed no significant dispositional interactions between methadone and ethanol. BAC decreased after alcohol administration during peak methadone plasma levels. Clinical observation is that alcohol-abusing opioid-maintained patients have increased withdrawal between daily doses.	(184–189)
Amitriptyline	Increase	Amitriptyline was reported to decrease methadone clearance. It increases plasma AGP, thus increasing methadone binding.	(53,143,157)
Amprenavir	Decrease	A 35% decrease of methadone plasma levels has been observed. An open label, within-subject pharmacokinetic study showed a 13% decrease in R-methadone AUC.Amprenavir may induce CYP P450 enzymes. Fosamprenavir, a pro-drug of amprenavir, is rapidly and extensively converted to amprenavir after oral administration.	(65,90,93)
ASA	Not studied	Methadone administration decreased ASA metabolism by 50%.	(128)
Atazanavir	No effect	No changes were found in pharmacokinetic parameters of methadone after atazanavir therapy for 14 days in 16 patients. No clinical signs of withdrawal or excess were observed.	(94)
Benzodiazepine and Diazepam	No effect	In benzodiazepine abusers, methadone therapy may not be effective because the abusers are seeking a different effect from that of methadone. Pharmacodynamic interactions between benzodiazepines and opiates can lead to respiratory depression and potentially cause coma and death.	(144–149,151,152)
Buprenorphine	No effect	*In vitro* study suggests that, although buprenorphine and its major metabolite, norbuprenorphine, are inhibitors of CYP 2D6 and 3A4, at therapeutic concentrations they are not predicted to cause clinically important drug interactions with other drugs metabolized by major hepatic P450 enzymes.	(178–180)
Burns	Decrease	Burn patients suffer from a reduced volume distribution and absorption rate of oral drug. AGP levels increase and can remain elevated for 20 days after injury. Increased dosages may be necessary to alleviate withdrawal symptoms. Significant predictors of clearance in the early post-burn period were days post injury, age, and serum albumin.	(227,228)
Cannabis	Not studied	Trough plasma (R)-and (S)-methadone are significantly associated with cannabis use and higher methadone dose.	(190)
Carbamazepine	Decrease	2 cases reported decreased plasma levels of methadone in coadministration with carbamazepine. 1 case reported naloxone-reversible respiratory depression in a patient after discontinuation of carbamazepine.	(133–135)
Cimetidine	Not studied	Case report of opiate toxicity after beginning cimetidine therapy in an elderly man. Cimetidine inhibited *in vitro* N-demethylation but this is not a major metabolic pathway.	(175,176)
Ciprofloxacin	Increase	Case report of respiratory depression after initiation of ciprofloxacin treatment. The authors suggested that the mechanism is inhibition of CYP 1A2 and 3A4 by ciprofloxacin.	(108–110)
Cocaine	Decrease	In a study of the interaction between cocaine and methadone in 39 individuals who were maintained on varying doses of methadone, cocaine use decreased the methadone AUC_{0-24} with a corresponding increase in oral clearance and significantly lower methadone $C_{24\,h}$. The authors suggested that there may be an induction of CYP 3A4 by cocaine.	(191)
Delavirdine	Increase	Methadone clearance was decreased and the elimination half-life was increased after administration of delavirdine. No toxicity was reported over 7 days but patients should be closely observed after beginning treatment with delavirdine.	(76)
Desipramine	No effect	Methadone affects levels of desipramine. There was an observed increase in desipramine levels from 72.6–168.9% in five patients. Methadone may impair hydroxylation of desipramine.	(158,159)

Table 1. Continued

Drug	T½ Methadone	Comments	References
Dextromethorphan	Not studied	Delirium was reported in an elderly woman taking both methadone and dextromethorphan. Symptoms did not resolve when methadone was decreased but did resolve after 1 week following discontinuation of dextromethorphan. In another study of 10 opiate-dependent men, no serious adverse effects were reported.	(181,182)
Diclofenac	No effect	No significant change was found in 16 patients who were administered both methadone and diclofenac.	(129,130)
Didanosine and Stavudine	No effect	Methadone is not altered in the presence of these drugs, but didanosine and stavudine levels are reduced by 63% and 23%, respectively. Methadone lowers the absorption rate of both drugs. Increased bioavailability is observed with enteric-coated didanosine tablets in MMT patients.	(67,68)
Disulfiram	No effect	Although disulfiram enhances N-demethylation of methadone there was no significant interaction between disulfiram and methadone.	(188)
Efavirenz	Decrease	Efavirenz induces CYP P450 enzymes, leading to withdrawal symptoms in methadone-maintained patients.	(79–81)
Estrogen	Decrease	Estrogen tends to increase methadone clearance.	(143)
Ethnicity	Variable	Although methadone-AGP binding in ethnically different groups has not been reported it has been studied using other drugs. Two studies evaluated the AGP binding properties between racially distinct individual using drugs other than methadone. In both cases, Caucasians had a lower percentage of bound drugs than both Blacks and Chinese subjects.	(37,207)
Etravirine (TMC125)	No effect	*In vitro*, etravirine is predominantly metabolized by CYP 3A4 and 2C9/18/19. Etravirine is an inducer of CYP 3A4 and a weak inhibitor of 2C9, 2C19 and P-gp. No clinically relevant changes in methadone pharmacokinetics were observed.	(82,83)
Fluconazole	Decrease	In a study of 13 patients receiving fluconazole, significant increases were observed in methadone AUC, C_{max}, and C_{min} and a decrease in oral clearance. Respiratory depression was observed in a susceptible patient in one case report. Fluconazole is an inhibitor of both CYP 3A4 and 2C9	(111–113)
Flunitrazepam	Increase	Flunitrazepam interacts with methadone in a manner that may increase blood plasma concentration.	(144,153–155)
Fluoxetine	Variable	Fluoxetine increases plasma concentrations of the (R) - methadone only. Two studies found no clinical interaction between the two drugs. Fluoxetine inhibits CYP 2D6.	(26,163,167)
Fluvoxamine	Decrease	Fluvoxamine increases both (R)- and (S)-methadone in six addict patients. Fluvoxamine inhibits CYP 1A2 that metabolizes both enantiomers.	(162–164,166,167)
Fusidic acid	Decrease	Methadone maintained patients experienced under dosage of methadone during fusidic acid treatment. The half-life of fusidic acid decreased in these patients. Fusidic acid has a time-dependent effect on CYP P450 enzyme system.	(114,115)
Gender	Variable in females	AGP binding capacity was measured in both females and males. The values obtained were 2.79 ± 0.59 mg/g and 2.37 ± 0.29 mg/g respectively. It is possible that AGP-bound drugs in females have a reduced level of free drug. No significant difference in elimination was found in a small study.	(53,208,209)
Grapefruit Juice	No effect	Moderate increase in bioavailability of methadone. Not expected to be clinically significant although caution is recommended.	(195)
Hematocrit increased	Decrease	Increased hematocrit causes an increase of free fraction of methadone and thus increases methadone clearance by the liver.	(143)
Heroin	Not studied	Using methadone and heroin simultaneously may increase risk of rhabdomyolysis and ischemic stroke.	(192)
Indinavir	No effect	An i*n vitro* study found that indinavir inhibits N-demethylation. Another study in 12 subjects showed no significant effect on the pharmacokinetic parameters of both methadone and its metabolite EDDP.	(95,96)
Itraconazole	Decrease	Itraconazole is a CYP 3A4 inhibitor and can lead to increased the plasma methadone level	(117)
Ketoconazole	Decrease	Methadone plasma levels were increased by 35% in 34 patients. Ketoconazole is an inhibitor of CYP P450 hepatic enzymes.	(111,119)

Table 1. Continued

Drug	T½ Methadone	Comments	References
Lamivudine	No effect	The interaction is unlikely as methadone and lamivudine are eliminated via different pathways. The former is eliminated by hepatic metabolism and the latter has renal elimination.	(71,72)
Liver disease	No effect	Maintenance dosage need not be changed in stable chronic liver disease. A suggested explanation is that injury to the drug metabolizing system is offset by damage to the capacity of the liver to store and release unchanged methadone.	(229,230)
Lofexidine	Not studied	Lofexidine is a α_2-adrenergic receptor agonist commonly used to alleviate physical symptoms of heroin and opiate withdrawal. Assessment of performance revealed that there was a statistically significant decrease in cognitive function only for the most complex activities, such as mathematical processing. Significant changes in hemodynamic and cognitive efficiency were observed with coadministration of lofexidine and methadone compared with methadone alone.	(196)
Lopinavir	Decrease	The mean AUC of methadone decreased in two studies. Opiate withdrawal symptoms were increased only in one study. Suggested mechanism is induction of CYP 3A and 2D6 by lopinavir.	(97,98)
Macrolide Antibiotics:Clarithomycin, Erythromycin, Troleandomycin, Spiramycin and Josamycin	Variable	All 5 listed macrolides increase AGP levels and lead to decreased methadone plasma levels. Specifically, troleandomycin inhibited EDDP and EMDP formation by >70%. It was also found that troleandomycin inhibits CYP 3A function in the liver.	(120,121)
Malignant Disease	Increase	Methadone clearance is low because cancer patients have increased AGP. Methadone is highly bound to AGP and thus the free fraction of methadone is less.	(231)
Menstrual cycle	Decrease on day 4	AGP concentrations were measured in 9 patients during their menstrual cycle. AGP levels were significantly higher on day 4 than on other measured days. AGP increase may be due to hormonal changes during the month. Increase in AGP may decrease free fraction of methadone	(210)
Mibefradil	Increase	Mibefradil inhibits CYP 3A4 enzymes, which may result in an increase of plasma methadone levels. Mibefradil binding to AGP causes binding competition between concomitant medications.	(141)
Naloxone	No effect	Naloxone-methadone is a classical antagonist vs. agonist reaction. Withdrawal reaction does occur and plasma levels of methadone are not affected.	(114)
Naltrexone	Not studied	Naltrexone, a long acting μ receptor full antagonist, blocks the opioid receptors that modulate the release of dopamine in the brain reward system and therefore blocks the rewarding effects of both heroin and alcohol. Naltrexone has been used in rapid detoxification from methadone.	(183)
Nelfinavir	Decrease	One case of opioid withdrawal was reported in a patient on nelfinavir and stavudine. Two other studies report no withdrawal symptoms but a decrease in methadone AUC, C_{max}, and C_{min} in patients of nelfinavir alone. Suggested mechanisms include nelfinavir binding to AGP and both induction and inhibition of P-gp and the CYP P450 system.	(78,99–101)
Nevirapine	Decrease	Six independent studies and case reports found withdrawal symptoms after nevirapine and methadone treatments. Nevirapine is a potent inducer of CYP P450 enzymes.	(84–86,89)
Nicotine	No effect	There is no evidence of pharmacokinetic interaction between methadone and nicotine although a pharmacodynamic interaction has been reported	(193,194)
Nifedipine	No effect	Methadone inhibits nifedipine oxidation by a mixed-type inhibition with a K_i value of 100 μmol/L	(142)
Obesity	Decrease	Two studies found that AGP levels were higher in obese individuals due to increases of stress and stress-related diseases. Obese patient on methadone may need better regulation due to increased AGP levels.	(212–216)
Olanzapine	Not studied	No change in methadone plasma levels to dose ratio in 15 patients. Withdrawal syndrome was not observed in any patients.	(173)
Omeprazole	Increase	An increase of 54% of methadone plasma levels was found. Omeprazole interferes with the H+/K+ ATPase proton pump and increases gastric pH. Changes in gastric microenvironment alter methadone's absorption capabilities and lead to increased methadone plasma levels.	(131,132)

Table 1. Continued

Drug	T½ Methadone	Comments	References
Paroxetine	Increase	Increased methadone concentrations were observed as a result of an inhibitor of CYP 1A2, 2C9, 2C19, 2D6 and 3A4.	(168)
Peginterferon alpha-2a	No effect	No appreciable effect on the pharmacokinetics of methadone or Peginterferon alpha-2a was found in a study of 24 patients with hepatitis C.	(197–200)
Phenobarbital and barbiturates	Decrease	Chronic intake of phenobarbital may accelerate the metabolism of methadone and induce withdrawal symptoms in methadone maintained patients. Barbiturate is thought to create the cycle of intoxication and withdrawal in heroin users.	(135,138–140)
Phenytoin	Decrease	Phenytoin causes an increased methadone clearance, probably by inducing CYP 3A4	(136)
Pregnancy	Decrease	The fetal unit and placenta metabolizes methadone, thus enhancing methadone clearance. Clearances of both total and unbound methadone increased even after weight adjustment. Higher elimination rate constant and lower half-life in pregnant patients compared to controls has been reported. Withdrawal may occur. The suggested therapy is to divide methadone administration without increasing the daily dose.	(18,63,217–222,224)
Quetiapine	Not studied	Quetiapine increased plasma (R)-methadone but not (S)-methadone concentration. This increase was likely as a result of an interaction with CYP 2D6 and/or P-gp. None of the patients reported signs of opioid overdose.	(174)
Quinidine	Not studied	Quinidine increased plasma methadone concentrations during the absorptive phase after oral administration. This was most likely due to inhibition of intestinal P-gp. C_{max} and methadone AUC were unchanged.	(61)
Rifabutin	Variable	Although rifabutin may induce CYP 3A4, there is a large interindividual variability among patients. Patients with a significant decrease in plasma methadone concentration may be attributed to rifabutin's CYP 3A4 induction.	(122–124)
Rifampin	Variable	Rifampin administration in patients causes a decrease in methadone plasma levels. Some patients showed reduced elimination half lives, while others were prolonged or unchanged. Explanations include induction of hepatic enzymes and altered distribution of methadone.	(13,125,126)
Ritonavir	Variable	Three studies found decreased levels of plasma methadone, with no withdrawal syndromes. Despite this, one study found that ritonavir inhibits N-demethylation *in vitro*.	(95,97,98,103,105)
Saquinavir	Variable	One study found a decrease in methadone AUC_{0-24} with saquinavir/ritonavir therapy; however one study found no effect. Both studies found decreased protein binding of methadone. Interaction not likely to be clinically significant. Saquinavir inhibits N-demethylation *in vitro*.	(95,103,107)
Sepsis	Variable	Septic patents have increased AGP levels, which would result in a reduced level of unbound methadone. Liver and kidney malfunction, which may alter production of acute phase reactants, is also common.	(232,233)
Sertraline	Increase	Patients on both medications had a mean increase in methadone plasma levels of 26%. None of the patients had withdrawal symptoms. Sertraline inhibits CYP 2D6 and 1A2.	(169–171)
Spironolactone	Decrease	Spironolactone tends to increase methadone clearance. Spironolactone has been reported to be an inducer of hepatic-metabolizing-enzymes.	(177)
St. John's wort	Decrease	A decrease in methadone plasma levels was observed after treatment with St. John's wort. The anti-depressant may induce CYP 3A4 activity.	(160,161)
Tenofovir	No effect	No significant changes in methadone AUC or C_{max} were seen after administration of tenofovir DF.	(69)
Transplants	Decrease	AGP concentrations are elevated post surgery compared to pre surgery. Increased AGP levels may result in a decrease of methadone plasma levels.	(234–236)
Urinary pH (acidic)	Decrease	Acidic urine tends to increase urinary clearance of methadone. A decreased EDDP/ methadone ratio occurs. Methadone is partially reabsorbed by a pH dependant process. Urine pH is the major factor in renal clearance of methadone. Below pH 6.0, renal clearance becomes important.	(19,225,226)

Table 1. Continued

Drug	T½ Methadone	Comments	References
Urinary pH (basic)	Increase	Alkaline urine tends to increase the elimination half-life of methadone.	(19,225,226)
Valproic acid	No effect	Valproic acid treatment seems to be effective for methadone-maintained patients who experience seizures, compared to phenytoin and carbamazepine. Valproic acid, however, may cause hepatic toxicity or hemorrhagic pancreatitis.	(133,137)
Venlafaxine	Increase	Effective metabolism and clearance of both methadone and venlafaxine are dependent on CYP 3A4. Serotonin syndrome has been observed when both these medications have been prescribed.	(108,109,172)
Verapamil	Decrease	Verapamil tends to increase methadone clearance.	(143)
Voriconazole	Decrease	Increase in methadone is attributed to the stereoselective inhibition of methadone metabolism by voriconazole through its inhibition of CYP 2C19. Steady-state voriconazole pharmacokinetics is not affected.	(127)
Withdrawal/overdose	Variable	Several drugs are able to induce or inhibit the activity of CYP P450 enzymes involved in methadone metabolism. Combining methadone with an inhibitor increases the risk of torsades de pointes. Inducers result in a reduced methadone plasma concentration, whereas inhibitors increase methadone plasma levels. The former results in clinical withdrawal symptoms and the latter potentiates overdose symptoms. Unbound methadone can be significantly decreased in patients showing signs of withdrawal because of a significant rise in AGP concentration	(55)
Zidovudine	No effect	Zidovudine plasma levels increase with concomitant administration of methadone. Methadone is thought to inhibit glucuronidation and renal clearance of zidovudine.	(73–75)

KEY REFERENCES: Methadone and drug-drug interactions

(See Excel Sheet 1 for more references)

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CHAPTER 8: METHADONE FOR ANALGESIA IN PEDIATRIC PATIENTS

This chapter reports on the use of methadone for pediatric cancer patients or pediatric patients that have illness accompanied by persistent pain. Neonates, children, adolescents and young adults that have cancer or life-threatening illness have distinctive medical and psychosocial needs that should be met with palliative care that reflects advances in pain and symptom management for this age spectrum (Pilkey et al., 2013; Pritchard et al., 2011). Moderate to severe acute cancer pain requires strong pain medication and approximately 60%–90% of pediatric patients with life-limiting or life-threatening diseases receive opioids at the end of life (Friedrichsdorf and Postier, 2014; Zernikow et al., 2009). Importantly, methadone is available in liquid formulation and this facilitates the administration of extended pain medication for children unable to swallow pills (Friedrichsdorf and Kang, 2007). However, pediatric oncologists may be reluctant to use methadone as few studies describe the use of methadone for analgesia in pediatric patients and most lack familiarity with its use (Roth et al., 2013).

- The mean $t_{1/2}$ in children aged 1 to 18 years is 19 ± 14 h (range 4-–62 h); for neonatal patients a slower mean $t_{1/2}$ of 44 ± 22 h (3.8–2 h) has been reported (reviewed in Zernikow et al., 2009)
- A switch to levamethadone or methadone in pediatric patients is usually done in hospital (Zernikow, 2009); however, rotation to methadone can be done safely with close monitoring in outpatient settings as well (Davies et al., 2008)
- Converting pediatric patients from one opioid to methadone requires close observation for delayed sedation, which may occur 3 to 5 days following the

initiation of the drug. Dose intervals need to be decreased after the initial 1 to 2 days of treatment to avoid late sedation (Friedrichsdorf and Kang, 2007)

- Reported conversion ratios of morphine equivalent daily dose/methadone daily dose ranged from 1: 2 in one pediatric cancer patient with sudden pain crisis just prior to death, to 60: 1 in a pediatric patient who had been treated with opioids for months (Davies et al., 2008)
- Pediatric patients with life-limiting illnesses that are given morphine for analgesia may develop hyperalgesia, allodynia, and myoclonus; for these patients, it may be beneficial to switch to methadone or fentanyl to allow morphine 3-glucuronide metabolites to clear from the cerebral spinal fluid (Friedrichsdorf and Kang, 2007)
- Only oral methadone and morphine can be provided as immediate release preparations which can be graduated in a syrup preparation, according to weight (Mercadante and Girratano, 2014)
- Methadone is effective for pediatric cancer patients with neuropathic pain or nociceptive pain unresponsive to other opioids; it also prevents opioid withdrawal in these patients (Anghelescu et al., 2011)
- WHO recommends the following opioid switching tables and dose ratios for opioid-naïve pediatric patients aged 1–12 years (Tables 8.1 and 8.2; WHO, 2012)

Table 8.1 WHO opioid conversion table for opioid-naïve pediatric patients (WHO, 2012)

Table 3.4 Starting dosages for opioid analgesics in opioid-naive children (1–12 years)

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	1–2 years: 200–400 mcg/kg every 4 hrs 2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg)
	Oral (prolonged release)	200–800 mcg/kg every 12 hrs
	IV injection[a]	1–2 years: 100 mcg/kg every 4 hrs 2–12 years: 100–200 mcg/kg every 4 hrs (max 2.5 mg)
	SC injection	
	IV Infusion	Initial IV dose : 100–200mcg/kg[a], then 20–30 mcg/kg/hr
	SC infusion	20 mcg/kg/hr
Fentanyl	IV injection	1–2 mcg/kg[b], repeated every 30–60 minutes
	IV infusion	Initial IV dose 1–2 mcg/kg[b], then 1 mcg/kg/hr
Hydromor-phone[c]	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)
	IV injection[d] or SC injection	15 mcg/kg every 3–6 hrs
Methadone[e]	Oral (immediate release)	100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially)[f]
	IV injection[g] and SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hours (max 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hours

[a] Administer IV morphine slowly over at least 5 minutes.

[b] Administer IV fentanyl slowly over 3–5 minutes.

[c] Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.

[d] Administer IV hydromorphone slowly over 2–3 minutes.

[e] Due to the complex nature and wide inter-individual variation in the pharmacokinetics of methadone, methadone should only be commenced by practitioners experienced with its use.

[f] Methadone should initially be titrated like other strong opioids. The dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation. From then on dosage increases should be performed at intervals of one week or over and with a maximum increase of 50%.

[g] Administer IV methadone slowly over 3–5 minutes.

Table 8.2 WHO dose ratios for switching between parental and oral dosage forms in pediatric patients (WHO, 2012)

Table 3.5 Approximate dose ratios for switching between parenteral and oral dosage forms

Medicine	Dose ratio (parenteral : oral)
Morphine	1:2 – 1:3
Hydromorphone	1:2 – 1:5[a]
Methadone	1:1 – 1:2

[a] Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.

KEY REFERENCES: METHADONE FOR ANALGESIA IN PEDIATRIC PATIENTS
(See Excel Sheet 1 for more references)

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CHAPTER 9: METHADONE FOR ANALGESIA IN OPIOID-DEPENDENT PATIENTS

Upon completion of this chapter, health care providers will be aware of issues surrounding pain management in opioid-tolerant and opioid-dependent patients with cancer pain and chronic non-cancer pain. The number of patients on methadone maintenance programs has increased globally, and pain, psychosocial management, and additional screening strategies are needed for this patient population (Huxtable et al., 2011Liberto and Fournili, 2013). However, a wide variety of pain management strategies and ambiguity exists between health care providers treating both chronic pain and addiction (Berget et al., 2009). Nonetheless, a comprehensive treatment plan with firm boundaries, which addresses both chronic pain and substance abuse, must be developed before medication is provided (Dian and Hawley; on behalf of the CPSBC, 2010).

- NOUGG recommends a comprehensive inquiry and screening process about substance use as a history of addiction to any substance is a risk factor for prescription opioid misuse and addiction. In addition, alcohol and other sedating drugs can have dangerous interactions with opioids (Kahan et al., 2011)

- Methadone or buprenorphine treatment is advised for opioid-addicted patients with chronic non-cancer pain that need outpatient tapering (Kahan et al., 2011)

- Methadone should be considered early for the treatment of cancer pain in patients on MMT. Should clinicians opt to use an opioid other than methadone as an analgesic in these patients, methadone should be continued, even if doses of the new opioid are rapidly escalated, to avoid pain exacerbation (Manfredi et al.,

2001). If the methadone dose is increased, this should be done in consultation with the registered prescriber/addiction medicine specialist (Huxtable et al., 2011)

- Frequent urinary drug testing and counseling is recommended (Kahan et al., 2011)
- Opioid-dependent pregnant women with chronic non-cancer pain should receive methadone treatment (Kahan et al., 2011)
- A contract between the patient and the healthcare team may prove helpful (North London Cancer Network, 2010)

KEY REFERENCES: METHADONE FOR ANALGESIA IN OPIOID-DEPENDENT PATIENTS
(*See Excel Sheet 1 for more references*)

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CONCLUSION

A large body of evidence demonstrates that methadone is efficacious for controlling several cancer pain types and chronic non-cancer pain, while an overwhelming body of experience shows that methadone plays a significant role in pain management, particularly for patients experiencing neuropathic pain or chronic pain. However, methadone is weakly recommended for chronic-non cancer pain in several internationally recognized guidelines and recommendations of methadone use for cancer pain are rare or are only described in regional- or institution-based guidelines. This is likely due to unresolved issues surrounding methadone safety, the paucity of randomized controlled trials that investigate methadone for cancer pain, adverse effects, and drug-drug interactions. Of further concern is the growing need to address pain management in opioid-dependent patients, yet performing randomized controlled trials with this patient group continues is challenging. Formulary availability and regulations surrounding methadone use hamper progress for optimal pain management in Canadian palliative care settings and in similar care settings for patients living and dying with pain around the world.

ONLINE RESOURCES AND SUPPORTIVE MATERIALS

Academic Pain Directors of Canada http://fhswedge2.mcmaster.ca/apdocs/
Alberta Health www.health.alberta.ca
British Columbia Ministry of Health www.gov.bc.ca/health/
Canadian Virtual Hospice www.virtualhospice.ca
Canadian Institute for Health Information www.cihi.ca
Canadian HealthCare Network www.canadianhealthcarenetwork.ca/
Canadian Hospice Palliative Care Association www.chpca.net/
Canadian Network of Palliative Care for Children cnpcc.ca/
Canadian Pain Society www.canadianpainsociety.ca/en/index.html
Canadian Pain Coalition www.canadianpaincoalition.ca
Canadian Partnership Against Cancer www.partnershipagainstcancer.ca/
Canadian Pharmacists' Association www.pharmacists.ca/
Canadian Society for Palliative Care Physicians www.cspcp.ca/
Collège des médecins du Quebec www.cmq.org
College of Physicians and Surgeons of Alberta www.cpsa.ab.ca/
College of Physicians and Surgeons of British Columbia www.cpsbc.ca
College of Physicians and Surgeons of Manitoba cpsm.mb.ca
College of Physicians and Surgeons of New Brunswick www.cpsnb.org/
College of Physicians and Surgeons of Newfoundland and Labrador www.cpsnl.ca
College of Physicians and Surgeons of Nova Scotia www.cpsns.ns.ca
College of Physicians and Surgeons of Ontario www.cpso.on.ca
College of Physicians and Surgeons of PEI cpspei.ca
College of Physicians and Surgeons of Saskatchewan www.cps.sk.ca/
Controlled Drugs and Substances Act laws-lois.justice.gc.ca/eng/acts/C-38.8/
Federal Drug Administration www.fda.gov/
Federation of Medical Regulatory Authorities of Canada www.fmrac.ca
First Nations and Inuit Health www.hc-sc.gc.ca/fniah-spnia/index-eng.php
General Practice Physicians in Nunavut www.nunavut-physicians.gov.nu.ca/
Health and Community Services-Newfoundland and Labrador
www.health.gov.nl.ca/health
Health Canada www.hc-sc.gc.ca/index-eng.php
Health Saskatchewan www.health.gov.sk.ca/
Institute for Safe Medication Practices Canada www.ismp-canada.org/
International Association for Hospice & Palliative Care www.hospicecare.com
Manitoba Health www.gov.mb.ca
Methadone Program-Health Canada www.hc-sc.gc.ca/hc-ps/substancontrol/exemptions/methadone-eng.php
Michael G. DeGroote National Pain Centre
www.nationalpaincentre.mcmaster.ca/index.html
National Institutes of Health nih.gov
New Brunswick Health www2.gnb.ca/content/gnb/en/departments/health.html
Northwest Territories Medical Association www.nwtma.ca
Northwest Territories Health and Social Services
www.hlthss.gov.nt.ca/english/default.htm

Nova Scotia Department of Health and Wellness novascotia.ca/dhw/
Nunavut Health Care Plan gov.nu.ca/health/information/nunavut-health-care-plan
Ontario Ministry of Health and Long-term Care www.health.gov.on.ca/
Prince Edward Island Department of Heath and Wellness www.gov.pe.ca/health/
Régie de l'assurance maladie Québec www.ramq.gouv.qc.ca/en/citizens/health-insurance/pages/health-insurance.aspx
Royal College of Physicians and Surgeons of Canada
www.royalcollege.ca/portal/page/portal/rc/public
World Health Organization www.who.int
Yukon Health and Social Services www.hss.gov.yk.ca/
Yukon Medical Council www.yukonmedicalcouncil.ca