

Dear Dr.

Re: Methadone License

Thank you for your interest in applying for a methadone license for your palliative care patient. Included in this package are:

1. Methadone exemption application
2. An article by one of our former palliative care consult physicians, Dr. Anna Taube, regarding the clinical management of patients receiving methadone (updated by myself & Dr. Ingrid de Kock)
3. Review of Methadone drug interactions (inhibitors and inducers of Methadone metabolism)
4. A list of several Edmonton pharmacies that stock methadone

Please follow the following procedure:

1. Fill out the methadone exemption application
2. Fax and mail a copy to Health Canada (directions are on page 3 of the application form)
3. Fax a copy to Mr. Clarence Wepler of the College of Physicians and Surgeons of Alberta at (780) 429-1981 (phone number (780) 969-4946). If Mr. Wepler is away, Dr. Janet Wright of the Triplicate Prescription Program (same Fax and Phone number) will be available to answer questions

On receipt of your application, the College will review the application and provide a letter of support for your license to Health Canada. If your patient has been seen by our service, the consultant involved will call the College of Physicians and Surgeons of Alberta and let Mr. Wepler or Dr. Wright know to expect your application.

Sincerely,

M. Mirhosseini

Dr. Mehrnoush Mirhosseini
Physician Consultant



PROTECTED WHEN COMPLETED/ PROTÉGÉ LORSQUE REMPLI

Methadone

Exemption Application Application pour une exemption

1. IDENTIFICATION

Please Print / s.v.p. en lettres moulées

| | | |
|---|--|---------------------|
| Applicant: Physician/ Médecin <input type="checkbox"/> Veterinarian/Vétérinaire <input type="checkbox"/> Dentist/Dentiste <input type="checkbox"/> | | |
| Surname/ Nom: | | Given Name/ Prénom: |
| Licence(s)/ License(s): | | |
| Specialty/Sécialité: | | |
| Post Graduate Training/ Formation professionnelle: | | |
| Primary Practice Address/Adresse du lieu d'exercice: | Institution: | |
| | Street/Rue: | |
| | Room/pièce: | |
| | City/Ville: | |
| | Province: | |
| | PostalCode/ Code postal: | |
| Telephone/Téléphone: | Fax/ télécopieur: | |
| E-mail Address/ Courriel: | | |
| Mailing Address (if different from above)/Adresse de correspondance (si différente) | | |
| Language / Langue | English <input type="checkbox"/> Français <input type="checkbox"/> | |

4. DECLARATION

By, this and under the condition that the released information is treated confidentially, I consent to the release from the licensing authority of the province or provinces in which I am registered and entitled to practice, to the Office of Controlled Substances of information from my personal file pertaining to the review of my application to prescribe methadone or to any other action related to this request for an exemption

Par la présente, et sous réserve que soit respecté leur caractère confidentiel, j'autorise le Collège des médecins de la / des provinces où je suis enregistré à dévoiler au Bureau des substances contrôlées toute recommandation ou tout renseignement contenu dans mon dossier personnel susceptible d'être utile à l'étude de ma demande d'exemption à prescrire la méthadone ou toute autre action pouvant être prise en rapport avec cette demande d'exemption.

| | | | |
|------------|--|-------|--|
| Signature: | | Date: | |
|------------|--|-------|--|

Please send the application to the address below:

**Methadone Programme
Evaluation and Authorization Division
Office of Controlled Substances
Health Canada
3rd Floor
123 Slater St
AL 3503B
Ottawa ON K1A 1B9**

A copy of the application may be faxed to (613) 952-8576, however, **the original must be sent by mail.** For further information, please contact the Evaluation and Authorization Division at (613) 946-5139 or toll free at 1-866-358-0453, by fax at (613) 952-8576 or by e-mail at exemption@hc-sc.gc.ca

Veuillez faire parvenir la demande à l'adresse ci-dessous :

**Programme de la méthadone
Division de l'évaluation et autorisations
Bureau des substances contrôlées
Santé Canada
3ième étage
123 rue Slater
IA 3503B
Ottawa ON K1A 1B9**

Il est à noter qu'une copie de la demande peut être envoyée par télécopieur au (613) 952-2196; l'**original doit cependant être envoyé par la poste.**

Pour plus d'information, veuillez communiquer avec la Division de l'évaluation et autorisations par téléphone au (613) 946-5139 ou sans frais au 1-866-358-0453, par télécopieur au (613) 952-2196 ou par courriel à exemption@hc-sc.gc.ca

Methadone-Dispensing Community Pharmacies

| | |
|--|--|
| <p>Location: Southside Dispensaries Ltd. (Cedars Professional Park) 2925 – 66 Street, T6K 4C1 Tel: 461-3021 Fax: 466-8402 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 0900 – 1720 Weekends, holidays: closed Delivery: yes, free, M>F</p> |
| <p>Location: Northside Market Drugs 10203 – 97 Street T5J 0L5 Tel: 422-1397 Fax: 426-6179 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 0830 – 1730 Sat: 0900 – 1500; Sun & holidays: closed Delivery: yes, free, M>S</p> |
| <p>Nolan Drugs 8901 – 118 Ave T5B 0T5 Tel: 477-2748 Fax: 479-4029 Continue to make liquid? yes Continue to make compounded capsules? no Continue to make compounded suppositories? no</p> | <p>Hours: Mon – Fri 9:00 – 7:00 Sat: 0900 – 1700 Sun & holidays: closed After Hours: 477-2748, will transfer to on call pharmacist cell phone. Delivery: yes, free within store hrs.</p> |
| <p>Parkdale Drugs 8111 – 118 Ave T5B 0R9 Tel: 477-1192 Fax: 477-5127 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 0900 – 1800 Sat, Sun & Holidays: 1000 – 1400 After Hours: 477-1192, will transfer to on call pharmacist cell phone. Delivery: yes, free within reasonable hrs. Late night will be delivered next day</p> |
| <p>Dolar Drug Marts 13211 – 132 Ave T8N 6G2 Tel: 455-0555 Fax: 452-4508 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 0900 – 2100 Sat: 0900 – 2000 Sun & Stat Holidays: 1000 – 1700 After Hours: 975-8258 Delivery: yes, free within reasonable hrs. Late night will be delivered next day.</p> |
| <p>Hawkstone Pharmacy Ste. 100, 1832 Lessard Road T6M 2W8 Tel: 433-3413 Fax: 438-1970 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 0900 - 2100 Sat: 0900 - 1800 Sun & Stat Holidays: 1000 – 1700 Delivery: yes, free within store hrs.</p> |
| <p>Medicine Shop, Millwoods 127 Milbourne Road East T6K 1P6 Tel: 461-8648 Fax: 461-8673 Continue to make liquid? yes Continue to make compounded capsules? yes Continue to make compounded suppositories? yes</p> | <p>Hours: M>F: 1000 - 1900 Sat: 1000 - 1500 Sun & Stat Holidays: Closed After Hours: 445-8385 Delivery: free, within reasonable hrs. Late night will be delivered next day.</p> |

- Metadol tablets available in 1,5,10, 25 mg
- If Methadone prescription is written for 1, 5, 10 or 25 mg, the pharmacy must dispense the Metadol product. Any other strength can be compounded and Alberta Blue Cross allows a compounding fee. This will vary according to the time spent to prepare the product.
- The cost of compounded products are significantly less than Metadol but there is higher potential for substance abuse.
- All methadone formulations are covered by Palliative Blue Cross
- Most pharmacies (i.e., Safeway) will be able to fill methadone prescriptions with 1-2 days notice
- All pharmacies listed here have an after-hours contact number or pager accessible through the listed phone number, or the patient's palliative home care nurse

Methadone: What is its Role in Cancer Pain Control?

By Anna Wreath Taube, MD, CCFP, FCFP

*Updated November 2009 by M. Mirhosseini MD, CCFP; I. de Kock, MBChB, DA(S.A.)
(With input from the physicians in the AHS - Edmonton Zone - Palliative Care Program)*

Case study:

Mr. Henderson, 63, presented with a very large right upper lobe non-small cell lung cancer mass and extensive right pleural metastatic disease.

He had two pain syndromes:

1. A somatic/visceral aching pain, reasonably well-localized to the right shoulder and right upper anteroaxillary thorax, and compatible with the known tumour sites. He rated this pain at 6-7/10 at rest, on a pain scale of zero to 10 (0 = best, 10 = worst).
2. A neuropathic pain, compatible with tumour invasion into the right brachial plexus, and characterized by lancinating pain shooting down the right medial forearm into the little and ring fingers (eighth cervical and first thoracic dermatomes), also rated 6-7/10 at rest. There were associated paresthesias in the involved dermatomes, and paresis of the corresponding myotomes. Additionally, this pain had a severe incident component (exacerbation with movement) rated at 10, such that Mr. Henderson could not use his right arm.

In the month preceeding palliative consultation:

- his OxyContin® (slow-release formulation) dose had tripled
- he was using five to seven breakthrough doses of immediate release oxycodone per 24 hours
- he was on gabapentin 1200 mg per 24 hours

In this article:

1. What are the indications for methadone use?
2. What are the advantages and disadvantages of methadone, compared to other opioids?
3. How can a patient be safely rotated to methadone from another opioid?

Why methadone?

Methadone is a synthetic opioid receptor agonist developed over 60 years ago. Its use subsequently declined after the implication of methadone in numerous fatalities, attributed to respiratory depression due to inadvertent overdoses.^{1,2} Over the past two decades, however, interest in methadone's usefulness in cancer pain management has steadily risen. The reasons for this resurging interest include methadone's effective analgesic action with less risk of opioid neuropsychiatric toxicity compared to other opioids, its longer duration of action as well as good oral bioavailability (80 %) ³. It may be particularly useful in cancer pain syndromes which are difficult to control and require higher doses of opioid therapy, such as neuropathic or incident pain.

What is opioid neurotoxicity?

This syndrome results from the build-up of toxic metabolites, and is characterized by any combination of manifestations listed in Table 1.⁴

Table 1: Manifestation of Opioid Neurotoxicity

Myoclonus

- progressing to grand mal seizures if unchecked

Delirium

- fluctuating cognitive impairment and level of consciousness
- changes in psychomotor behavior (hypo- or hyperactivity)
- delusions (often paranoia)

Hyperalgesia

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

Opioid neurotoxicity can severely compromise pain control and patient quality of life. Methadone's lower incidence of neurotoxicity is related to its lack of neuro-active metabolites (myoclonus with *high-dose parenteral* methadone has been reported.).^{5,6,7}

Mr. Henderson's first assessment:

History revealed:

- drowsiness
- frequent myoclonus
- cognitive impairment
- the presence of tactile and visual hallucinations

Physical examination revealed:

- somnolence
- a Folstein Mini-Mental Status Examination score of 23/30 (expected normal for his age and level of education is 27/30)⁸
- dehydration
- myoclonic jerks occurring every few minutes
- marked tenderness over the anteroposterior right shoulder and right upper anteroaxillary thorax
- no discernible right supraclavicular or axillary tumour but sensory and motor evidence of a right brachial plexopathy
- severe incident pain in the right arm

Impression:

- Mr. Henderson was clearly experiencing opioid neurotoxicity in the presence of both neuropathic and nociceptive pain syndromes.

Given the severity of his toxicity, Mr. Henderson required immediate opioid rotation:

- He was switched to immediate release hydromorphone (slow-release opioid preparations should not be used in poorly controlled pain, due to the difficulty of rapid dose titration).
- Rehydration to facilitate renal excretion of toxic metabolites was accomplished with subcutaneous hydration.
- Intermittent use of antipsychotic medication was necessary for 24 hours to control the hallucinations (Table 2).

Table 2: Management of opioid neurotoxicity

- Opioid rotation (decrease the new opioid equianalgesic dose by ~ 25-30 %, due to incomplete cross-tolerance between opioids)
- Hydration (~1.5-2.0 L/24h)
- Short-term antipsychotic use, if clinically indicated (haloperidol 1 mg orally/subcutaneously every hour as needed)

Mr. Henderson's follow-up:

Within 48 hours the toxicity resolved and his pain control substantially improved. Within ten days, however, both pains were again poorly controlled, with pain scores and breakthrough analgesic use returning to original levels. Symptoms of opioid toxicity reappeared, although less severely than previously seen. Due to the presence of severe neuropathic and incident pain, and the recurring problem of opioid toxicity, the decision was made to rotate Mr. Henderson to oral methadone. This was done over four days. Gabapentin adjuvant analgesia was simultaneously discontinued. By completion of the rotation to methadone, Mr. Henderson rated both pains at 0/10 at rest, and the incident component at 3/10; an acceptable level for him. He regained limited use of his right arm. Over the remaining month of his life breakthrough analgesia was very rarely requested or deemed necessary by nursing staff, and there was no recurrence of opioid toxicity.

What are the advantages of methadone?

1. NMDA receptor antagonism

As well as being an opioid receptor agonist, methadone is a N-methyl-D-aspartate (NMDA) receptor antagonist.⁹ The NMDA pathway is a major excitatory central nervous system (CNS) pathway involved in the neurobiology of pain.¹⁰ Methadone's ability to dampen this pathway's excitation may explain its superior analgesic activity and, possibly, its lower risk of opioid toxicity.¹¹ These properties may also reduce the need for adjuvant analgesia, as Mr. Henderson's case demonstrates. Clinical experience suggests that methadone is advantageous for difficult pain syndromes, but confirmation by appropriately designed studies is required.¹² Its effective analgesic action in non-neuropathic cancer pain refractory to other opioid agonists has also been reported.¹³⁻¹⁶

2. High oral/rectal bioavailability

Methadone has high oral bioavailability, and only slightly lower rectal bioavailability.^{17,18} Customized methadone suppositories (also administrable into colostomy sites) are simply and inexpensively made.¹⁸ A suppository requires approximately 30 minutes for complete absorption (based on clinical experience).

3. Option of subcutaneous administration

The subcutaneous route is sometimes needed if oral administration is not feasible. Until recently methadone was not commonly administered subcutaneously in Canada, due to reports of injection site irritation.¹⁹ Recent findings and experience have shown that this can be alleviated by administering methadone intermittently through a normal saline hypodermoclysis line.²⁰ The rate of hypodermoclysis depends on the patient's need for hydration. The equianalgesic ratio between oral and subcutaneous methadone dosing is not clear, but case reports mention using half of the oral dose in subcutaneous form.^{20,21} This ratio has been used in the Edmonton Zone Palliative Care Program but further dose adjustment and titration of methadone might be required. Titration of the dose will be guided by the patient's level of consciousness and level of pain control.²⁰

4. Long half-life

Methadone's long half-life leads to a longer duration of action than other immediate-release opioids (see below), with 8- or 12-hourly dosing offering the convenience of slow-release formulations.

5. Minimal dependence on renal elimination

In contrast to codeine, morphine, hydromorphone, oxycodone, and fentanyl (the only other opioids recommended in Canada for cancer pain control), methadone is minimally dependent on renal excretion.²² Methadone may be the opioid of choice in the setting of significant renal impairment regardless of the underlying pain syndrome. Methadone's primary route of elimination is hepatobiliary. Studies to date have implied its safe use in hepatic impairment, but careful monitoring is advisable.²²

6. Less constipating than other opioids

Like other opioids, methadone's side-effects include sedation, nausea, dry mouth, sweating, pruritus and risk of urinary retention. Methadone, however, may be less constipating than other opioids.²³ Patients treated with methadone often require much less laxatives^{24,25} and may experience less nausea and vomiting.²⁶

What are the disadvantages of methadone compared to other opioids?

1. Methadone has wide and unpredictable inter-individual variability in its half-life, causing a respiratory depression risk with unpredictable timing when initiating and titrating methadone therapy.

Methadone's half-life ($T_{1/2}$) and correlating duration of action vary between individuals, from six to 60 hours.²⁷ There is no laboratory test to determine a specific patient's $T_{1/2}$. Given the general pharmacokinetic principle that administration of four doses of a drug, at appropriate intervals, is needed for stable serum level attainment,²⁸ stability of an individual's methadone serum level may occur anywhere from 24 hours ($T_{1/2}$ of six hours) to 240 hours ($T_{1/2}$ of 60 hours). During methadone initiation and to a lesser extent during dose titration, the risk of respiratory depression and its timing are unpredictable.²⁹ For this reason the Edmonton Palliative Care Program suggests that rotation to methadone from another opioid is done over a minimum of four days in a controlled environment (see Mr. Henderson's methadone rotation below). In the home or an environment with less control, this could be done over a longer period according to the circumstances and comfort of the attending health care professionals. These timelines allow for the development of tolerance to respiratory depression. **Only physicians experienced in methadone use should initiate methadone therapy.** Once the rotation is completed, the titration of methadone according to analgesic need is identical to other opioids. In the home setting, **methadone rotation should only be undertaken if a responsible adult caregiver is present and vigilant throughout this period, and the rotation is closely monitored by Home Care nursing staff and the prescribing physician.** If these requirements can not be met, the rotation should be done in a controlled hospital setting.

2. Methadone can cause a prolonged QTc interval.

Recent literature points to the relative risk of prolongation of QTc interval by methadone.^{30,31,32} QTc prolongation can lead to torsades de pointes (TdP). TdP is a type of ventricular tachycardia³³ which is often self-limited, but if it persists, can lead to ventricular fibrillation, syncope and sudden death.³⁴ The proposed QTc interval threshold varies widely in the literature (as slow as 430 - 450 ms in males and 450 - 470 ms in females);^{30,35} the International Regulatory Guidance for Drug Development suggests that a sex-independent categorical threshold for QTc interval prolongation is 450 ms.³⁶ The available literature (not specific to the palliative population) points to a significant risk of sudden death at QTc intervals of > 500 ms.^{37,38,39} Some authors suggest discontinuation of methadone in this situation.^{40,41}

In the two studies in the cancer and palliative population, the incidence of QTc prolongation varies from 16-28 %, but the very few deaths reported did not correlate with a QTc > 500 ms.^{42,43} The clinical significance of QTc interval prolongation, the approach to screening for prolonged QTc intervals and monitoring QTc interval changes in palliative patients requiring methadone for pain control, is controversial and requires further clarification. Until future studies shed more light on the best approach to screening for QTc interval prolongation with methadone, we recommend the following to prescribing physicians:

- having a low threshold for performing ECG
- being aware and investigating for the predisposing/ risk factors for QTc prolongation
- streamlining the medications that are CYP 3A4 inhibitors (Appendix 1)
- streamlining the medications with negative inotropic effects (Appendix 1)
- preservative-free parenteral methadone formulation is available in some pharmacies. (Chlorobutanol, a common preservative in the currently available injectable methadone formulation, is a negative inotropic agent and would increase the chance of QTc prolongation).⁴⁴ We suggest checking with your local pharmacy.
- discussing the advantages and disadvantages of methadone treatment, and tailoring the treatment strategy to achieve an optimal balance between the patient's wishes, goals of care, symptom management and the intention to do no harm.

3. Physicians must obtain a special license to prescribe methadone.

A special license must be obtained either from the Healthy Environment and Consumer Safety Branch of Health Canada. Depending on the province, application is made either directly to Health Canada or through the Provincial College of Physicians and Surgeons. Obtaining the license can take several weeks.

4. Not all pharmacies dispense methadone.

Prescribing physicians must familiarize themselves with dispensing pharmacies.

What is the standard methadone rotation protocol/model?

There are at least 12 published conversion models for methadone rotation. In Edmonton, we prefer a rotation over at least four days.^{45,46} The equianalgesic ratio depends on the individual Palliative Care physician's choice of model. If using a four-day rotation, the non-methadone opioid dose is reduced each day by approximately one third of the original dose, and the equianalgesic dose of methadone is substituted. Methadone is usually prescribed at eight hourly dosing intervals. On day four methadone breakthrough doses replace the breakthrough non-methadone opioid.

Over a six-day rotation, the non-methadone opioid dose is reduced daily by one fifth of the original dose, with replacement of the breakthrough with methadone on day six.

Daily clinician assessment and individual dose titrations, depending on analgesic and side-effect profiles, are strongly advised.

Mr. Henderson's rotation to methadone:

Mr. Henderson was in hospital, permitting a four-day switch to methadone. At the time of rotation Mr. Henderson was using 24 mg of oral hydromorphone (HM) every four hours, or 144 mg per 24 hours. His breakthrough analgesic dose was 12 mg orally every hour as required.

- 144 mg oral HM/24h \approx 720 mg oral morphine/24h.
- Thus 72 mg of methadone/24 h or 24 mg orally every eight hours, is the tentative methadone target end dose. For most patients an eight-hour administration interval is appropriate on initiation.

Day 1:

1. Decrease HM by \sim 33% (8 mg per dose) to 16 mg orally every four hours. The 48 mg (8 mg by six doses/24h) reduction in HM/24h \approx 240 mg oral morphine/24h \approx 24 mg oral methadone/24h.
2. Start methadone at 8 mg orally every eight hours.
3. Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 2:

1. Decrease each HM dose by another 8 mg, to 8 mg orally every four hours.
2. Increase each methadone dose to 16 mg every eight hours.
3. Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 3:

1. Discontinue HM.
2. Increase each methadone dose to 24 mg every eight hours.
3. Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 4:

1. Discontinue HM for breakthrough pain.
2. Start methadone 7 mg every hour as needed for breakthrough pain.

There are two accepted rules for calculating breakthrough doses:

Rule 1: 10% of the 24h total of regular doses

Rule 2: $\frac{1}{6}$ of the 24h total of regular doses

What are the equianalgesic dose ratios between methadone and other opioids?

Table 3: Opioid equianalgesic doses

| Opioid | Oral | Subcutaneous |
|--|-------------|---------------------|
| Codeine | 100mg | 50mg |
| Morphine | 10mg | 5mg |
| Hydromorphone | 2mg | 1mg |
| Oxycodone | 5mg | 2.5mg |
| Fentanyl transdermal: See manufacturer's chart | | |
| Fentanyl infusion: 10 microgram (mcg) sc/24h ≈ 1 mg sc morphine/24 hour * | | |
| Methadone: morphine equianalgesic ratio is dose-dependent * | | |
| <p>* Only physicians experienced with these opioids should initiate their use.</p> <p>Note: - For opioids other than methadone, oral: parenteral ratio is 2:1 - For methadone, oral: parenteral ratio is not well established, but a ratio of 2: 1 has been used as a starting guideline.</p> | | |

In the Edmonton Zone – Palliative Care Program, the conversion ratio depends on the 24 hour oral morphine equivalent dose, the patient's setting and the physician's conversion model of choice.^{45, 46, 47} Even the most conservative equianalgesic ratio poses respiratory depression risk if the patient is switched abruptly from another opioid to methadone,²² underpinning the practice of the several-day rotation protocol. Palliative care physicians in Edmonton Zone Palliative Care Program will try to rotate the patients to methadone in a controlled setting (e.g. Tertiary Palliative Care unit) and the most commonly used conversion ratios are as follows:

- ✓ If patient's current dose of opioids is <100 mg oral morphine/day, a ratio of morphine : methadone , 5-10: 1 milligram for milligram may be used
- ✓ If patient's current dose of opioids is 100 - 1000 mg oral morphine/day, a ratio of morphine : methadone 10:1, milligram for milligram may be used
- ✓ If patient's current dose of opioids is > 1000mg oral morphine/day the ratio of morphine: methadone is highly variable but can range from 10 - 60:1 milligram for milligram.

Should methadone be an early opioid of choice?

Initially the Edmonton Zone – Palliative Care Program viewed methadone as a third or even fourth line opioid, to be used when sequential trials of high dose non-methadone opioid therapy did not achieve pain control or caused opioid toxicity. With increased experience over the last decade the practice is shifting to earlier initiation of methadone, especially for neuropathic and intractable pain syndromes.



Take-home message:

- ⇒ Methadone may be advantageous for difficult to treat pain syndromes such as neuropathic and incident cancer pain.
- ⇒ Methadone is the opioid of choice for patients with renal impairment.
- ⇒ Methadone equianalgesic ratio to morphine is not well established. The ratio considered during rotation from other opioids to methadone is dependant on many factors including the pre-rotation opioid dose, route of administration, and patients' previous use of opioids, liver and renal function, medication history, site of care for the patient, goals of care and many other factors.
Therefore only experienced physicians should initiate methadone therapy.
- ⇒ There is a risk of respiratory depression with methadone initiation and dose titration. Once the patient has been established on a stable dose of methadone, this risk is lower with further dose titrations.

References:

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Appendix 1

Adapted from :

Cruciani RA, Sekine R, Homel P, Lussier et al. Measurement of QTc in patients receiving chronic methadone therapy. *J of Pain Symptom Manage* 2005; 29:385-391.

Risk factors for QTc prolongation / torsades de pointes:

- Elderly women
- Concomitant use of drugs with potential to prolong QTc
- Family history of sudden death
- Metabolic abnormalities :
 - hypokalemia, hypomagnesemia, hypocalcemia, hypoxia, acidosis, hypothermia
- Endocrine disorders:
 - hypothyroidism, hyperparathyroidism, pheochromocytoma, hyperaldosteronism
- Cardiac conditions:
 - Advanced heart disease:
 - myocardial ischemia, myocardial infarction, myocarditis, bradyarrhythmia, complete atrioventricular (AV) block
 - Congenital and acquired long-QT syndromes
- Intracranial disorders:
 - subarachnoid hemorrhage, thalamic hematoma, cerebrovascular accident, encephalitis, head injury
- Nutritional disorders:
 - anorexia nervosa, starvation, liquid protein diets, gastroplasty and ileojejunal bypass, celiac disease
- CYP 3A4 inhibitors
 - Potent inhibitors:
 - Protease inhibitors: ritonavir, nelfinavir, indinavir
 - Macrolide antibiotics: erythromycin, clarithromycin, troleandomycin
 - Antifungal agents: ketoconazole, itraconazole
 - Less potent inhibitors: Saquinavir, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, clotrimazole

Potential of commonly used medications in HIV/AIDS and chronic pain patients to produce QT prolongation:

| | |
|------------------|--|
| Very probable: | quinidine |
| Probable: | pimozide, ziprasidone |
| Possible: | clarithromycin, erythromycin, pentamidine, chlorpromazine, haloperidol, olanzepine, risperidone, amitriptylene, desipramine, imipramine, sertraline, venlafaxine |
| Improbable: | fluconazole, levofloxacin, trimetropin-sulfamethoxazole, fluoxetine, paroxetine, sumatriptan, zolmitriptan, methadone |
| Very improbable: | azythromycin, ciprofloxacin, clindamycin |

Drugs associated with torsades de pointes:

Amiodarone, arsenic trioxide, bepridil, chlorpromazine, cisapride, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, mesoridazine, pmethadone, entamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine

METHADONE

This patient is receiving methadone
as an analgesic.

Drug interaction: 5 principles

Reminder: Methadone is metabolized by
CYP 450 3A4-2B6>2D6>>2C9, 2C19, 1A2.

EFFECTS OF ENZYME INDUCERS AND INHIBITORS

- 1- Adding an inhibitor to methadone: generally results in an ↑ in serum levels of methadone.
- 2- Adding an inducer to methadone: generally results in a ↓ in serum levels of methadone (↓ efficacy) **after 7-10 days**, unless the methadone dose is ↑ in anticipation of the interaction.
- 3- Adding methadone to an inducer: may result in decreased efficacy of methadone (insufficient dose), unless the initial methadone dose is ↑ in anticipation of the interaction.
- 4- Removing an inhibitor: methadone and an inhibitor have been co-administered for some time (steady-state reached) then suddenly the inhibitor is stopped. Anticipated result (**may be very rapid; few hours to several days**): ↓ in serum levels of methadone (possible ↓ in efficacy), ↑ metabolites.
- 5- Removing an inducer: methadone and an inducer have been co-administered for some time (steady-state reached) then suddenly the inducer is stopped. Anticipated result **after 2-3 weeks**: ↑ in the serum levels of methadone (possible ↑ in efficacy), ↓ metabolites.

**Contact a pharmacist regarding any suspected interaction,
to discuss proper procedures.**

Included are the principal, relevant drug interactions.

All efforts have been made to provide up-to-
date information at the time of publication.

Produced by **Annie Th  berge** (community representative)
and **Andr  e N  ron** (hospital representative), pharmacists.
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CHUS
Des gens de s  rie et d'expertise

| May ↑ serum levels of methadone (↑ efficacy/toxicity). | May ↓ serum levels of methadone (↑ methadone dose may be required). | May cause an unpredictable interaction (↓ or ↑ of methadone) |
|---|--|---|
| <ul style="list-style-type: none"> - Alcohol (acute ingestion) - Amiodarone (Cordarone™) - Sodium bicarbonate - Chamomile - Cimetidine (Tagamet™) - Ciprofloxacin (Cipro™) - ♥ Clarithromycin (Biaxin™) - Delavirdine (Rescriptor™) - Diazepam (Valium™) - Diltiazem (Cardizem™, Tiazac™) - Echinacea - ♥ Erythromycin (Erybid™, Eryc™) - Fluconazole (Diflucan™) - ♥ Fluoxetine (Prozac™) - Fluvoxamine (Luvox™) - Goldenseal - Cat's Claw - Indinavir (Crixivan™) - Isoniazid (Isotamide™, INH) - Itraconazole (Sporanox™) - Grapefruit Juice (6- 8 glasses/day) - ♥ Ketoconazole (Nizoral™) - Metronidazole (Flagyl™) - Moclobemide (Manerix™) - ♥ Paroxetine (Paxil™) - Potassium Citrate - Quinidine (Biquin Durules™, Quinidine) - ♥ Sertraline (Zoloft™) - Verapamil (Isoptin™) | <ul style="list-style-type: none"> - Alcohol (chronic ingestion) - Amprenavir (Agenerase™) - Abacavir (ABC, Ziagen™) - Ammonium Chloride - ■ Barbiturates: primidone (Mysoline™), phenobarbital - ■ Carbamazepine (Tegretol™) - ♥ Cocaine - Dexamethasone (Decadron™) - ■ Efavirenz (Sustiva™) - Fosamprenavir (Lexiva™) - ■ Lopinavir/Ritonavir (Kaletra™) - ■ Nelfinavir (Viracept™) - ■ Nevirapine (Viramune™) - ■ Phenytoin (Dilantin™) - Potassium Phosphate - ■ Ritonavir (Norvir™) - ■ Rifampicin (Rifampine, Rifadin™) - ■ Risperidone (Risperdal™) - Spironolactone (Aldactone™, Aldactazide™) - St. John's Wort - Tobacco (cigarette smoke) - Vitamin C (high doses) | <ul style="list-style-type: none"> - BZ's: alprazolam (Xanax™), flurazepam (Dalmane™), midazolam (Versed™) - ♦ Didanosine (ddI, Videx™ formulation) - Dextromethorphan - Nifedipine (Adalat™) - ♦ Stavudine (d4T) - TCA's: <ul style="list-style-type: none"> - ♥ Amitriptyline (Elavil™) - ▲♥ Desipramine (Norpramin™) - ♥ Imipramine (Tofranil™) - ♥ Nortriptyline (Aventyl™) - ▲ Zidovudine (AZT- Retrovir™, in Trizivir™ and Combivir™) |

Legend:

♥: Use this Rx with caution; may cause cardiac dysfunction (↑ Qtc/torsades de pointe) if used with methadone (use caution with methadone doses of > 300mg/day). ▲: Methadone may ↑ serum concentrations of the affected Rx. ■: This Rx may cause withdrawal symptoms. ♦: Methadone may ↓ serum concentrations of the affected Rx. Bupropion (2B6 substrate).