

# drug information perspectives

Volume 25, Number 2, 2005

## Editors

Barbara J. Cadario, B.Sc.(Hon), B.Sc.Pharm., M.Sc.  
Karen L.A. Wlock, B.Sc.(Pharm.)

## Contents

**Methadone**  
Dorothy Li, B.Sc.Pharm.

## Chairman, Medical Review

Laird Birmingham, M.D., M.H.Sc., F.R.C.P.(C)  
Department of Medicine  
St. Paul's Hospital

## METHADONE

**TRADE NAME:** Metadol

**CLASSIFICATION:** Narcotic analgesic (synthetic); diphenylheptane

### ACTION:

Methadone is a pure narcotic agonist, a diphenylheptane derivative structurally related to propoxyphene but unrelated to meperidine, fentanyl and morphine. Binds to mu opioid receptors in the central nervous system causing analgesia. Stimulation of mu1 causes supraspinal analgesia while mu2 mediates spinal analgesia, respiratory depression, and inhibition of gastrointestinal transit. Binds with lower affinity to the delta and kappa receptors. Therapeutic effects are primarily due to (R)-methadone which is 10-50 times as potent as (S)-methadone. In opioid-dependent patients, the binding of methadone to opioid receptors blocks the euphoric effects of heroin and other opioids and suppresses the withdrawal syndrome and narcotic craving at clinically adequate doses.

Direct action in the medulla or pons suppresses the cough reflex, resulting in antitussive action. (S)-methadone is an N-methyl-D-aspartate (NMDA) receptor antagonist. Methadone inhibits the reuptake of serotonin and norepinephrine. Direct stimulation of the chemoreceptor trigger zone causes nausea and vomiting. Histamine release can produce side effects of hypotension, tachycardia, sweating, flushed face, and wheezing.

### PHARMACOKINETICS:

**-Half-life:** (RS)-methadone 35 +/- 22 hours; (R)-methadone 37.5 hours; (S)-methadone 28.6 hours

**-Absorption:** Oral bioavailability 70-80% (range 36-100%). Time to peak: Oral liquid: 2.33 hr (range 1-4 hr). Oral tablets: 3 hr (1-5 hr)

**-Distribution:** Highly bound to tissue protein (71-87%) primarily to alpha1-acid-glycoprotein variant orosomucoid2 A and orosomucoid1 S. Also binds to albumin and lipoproteins. Widely distributed, mean distribution volume (Vd) 6.1 +/- 2.4 L/kg. Vd increases with chronic administration.

**-Metabolism:** Metabolized primarily by CYP 3A4 and secondarily by CYP 2D6, 2C8, 2C9, 2C18, 2C19 and 1A2 to inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (M1) and 2-ethyl-5-methyl-3,3-diphenyl-pyrrolidine (M2). Additional metabolites have been identified. Following one month of therapy the rate of metabolism may increase in up to 1/3 of patients.

## B.C. Drug and Poison Information Centre

1081 Burrard Street, Vancouver, B.C. V6Z 1Y6  
Phone: (604) 682-2344; Ext: 62126 Fax: (604) 806-8262

**-Elimination:** Eliminated by metabolism and renal mechanisms. Urinary excretion of methadone and M1 accounts for 17-57% of the administered dose. A decrease in urinary pH leads to decreased renal reabsorption. Total body clearance = 2.7 +/- 1.7 mL/min/kg.

**-Special populations:** Elderly have increased half-life. Increased half-life in severe liver impairment. Insignificant amounts are removed by haemodialysis and chronic ambulatory peritoneal dialysis.

Considerable interindividual variation in pharmacokinetics due to variable CYP activity, glycoprotein, urine pH, duration of therapy, and concurrent medications.

## **USES AND EFFICACY:**

### **Uses:**

-Detoxification or longterm maintenance treatment of **opioid-dependence**

-**Pain control** for acute cancer pain, palliative care, and in chronic pain disorders

### **Major clinical trials**

#### **Maintenance treatment of opioid dependence: versus naltrexone:**

In an observational study of 1503 heroin users in Italy, retention rates (an established outcome measure for heroin addiction) following one year of methadone maintenance, naltrexone or non-drug program were 40%, 18% and 15%, respectively. The relative risk of leaving treatment within one year was 0.46 (95% CI 0.40-0.53) for patients on methadone maintenance and 0.84 (95% CI 0.69-1.00) for patients on naltrexone compared to patients on the non-drug program. Patients taking at least 60 mg daily of methadone were more likely to remain in treatment than patients taking <30 mg daily.

#### **Maintenance treatment of opioid dependence: versus LAAM (not currently available in Canada):**

In a 17-week trial completed in the United States, 220 patients diagnosed with opioid dependence were randomized to receive levomethadyl acetate (LAAM), buprenorphine, high-dose methadone (60-100mg daily) or low-dose methadone (20mg daily). The mean number of retention days was significantly greater for high-dose methadone (105 days), LAAM (89 days) and buprenorphine (96 days) compared to low-dose methadone (70 days,  $P < 0.001$ ). Retention was significantly higher for the high-dose methadone group than for the LAAM group. Patients who received high-dose methadone, LAAM or buprenorphine submitted significantly fewer opioid-positive urine specimens than the patients who received low-dose methadone.

#### **Maintenance treatment of opioid dependence: combined with prescribed heroin:**

In a randomized, open-label, multicentre controlled trial of 549 treatment-resistant heroin addicts in the Netherlands, combined use of medical prescription heroin (inhalation or injection) and methadone for 12 months had an increased response rate compared to methadone alone. Outcomes were based on physical, mental and social measurement. However, 45-88% of subjects did not respond to coprescription of heroin, and within the heroin groups there was one heroin overdose, a car crash and one death. Longterm studies evaluating established outcome measures are required to determine the role of prescribed heroin in combination with methadone in this setting.

### **Clinical course**

**-Steady state drug concentrations:** 5-7 days.

**-Oral analgesic doses:** *Onset:* 30-60 min. *Peak analgesic effect:* 90-120 min. *Duration of analgesia from initial oral dose:* 4-6 hr. *Duration of action following repeated oral dosing:* 22-48 hours.

**-Opiate addiction:** *Suppression of miosis and narcotic withdrawal after oral doses:* >24 hours.

### **Place in therapy:**

**Detoxification of opioid dependence:** Methadone is most commonly used to relieve the symptoms of withdrawal from heroin, morphine, hydromorphone and meperidine addiction. Some clinicians prefer to approach addiction to propoxyphene, pentazocine, codeine or oxycodone by gradually decreasing the dose, or using clonidine.

Detoxification is used when maintenance methadone therapy is not an option, or when abstinence is the goal.

However, the failure rate and return to use of illicit drugs with detoxification can be higher than 90%, particularly when standard nonpharmacologic relapse prevention treatments are not used concurrently. Longterm methadone maintenance is more often used if there have been frequent relapses.

**Maintenance of opioid dependence:** Methadone maintenance is the most common treatment for opiate addiction. It is effective in decreasing the use of illicit drugs and the resultant morbidity, mortality and incarceration, reducing needle sharing, increasing access to healthcare, improving health, opening the way to social reintegration, increasing

likelihood of full-time employment, improving pregnancy outcomes, and decreasing cost to society. Methadone maintenance treatment decreases HIV risk behaviours and is causally related to lower rates of seroconversion. One-third of the patients on maintenance treatment do well, one-third alternate from good to bad performance, and one-third show no change from a lifestyle centered on drugs and crime. The studies comparing methadone to buprenorphine are limited by size, duration and variations in dosage regimens. There is no strong evidence to support methadone as being more effective than buprenorphine for the treatment of heroin-dependent patients or vice versa. Incarcerated patients who have a history of opioid abuse in the past but are not currently using opioids may be at increased risk for relapse and therefore are candidates for methadone maintenance therapy.

**Pain control:** Used for chronic management of cancer and nonmalignant pain. Useful if there is inadequate pain control, and in patients exhibiting opioid neuroexcitatory toxicity such as myoclonus, hallucinations, delirium and hyperalgesia. May be effective for neuropathic pain due to burn injuries, complex regional pain syndrome (Type I), myelomalacia, diabetic neuropathy, post herpetic neuralgia, or lumbar disc herniation.

### ***Advantages***

- Proven benefit in opiate addiction
- Since it does not cause euphoria or sedation when stable doses are reached, it does not interfere with activities of daily life
- As an analgesic, its structural difference makes it useful in patients with true allergy to morphine or hydromorphone
- Less expensive than other opioid analgesics.

### ***Disadvantages***

- In opiate addiction, it requires more frequent dosing compared to levomethadyl acetate (LAAM) (not currently available in Canada)
- May cause physical and psychological dependence
- Not a cure for opiate addiction; requires continued maintenance and physical dependence on opiates
- Overdose can be fatal
- Severe withdrawal symptoms if stopped abruptly
- Not available as a parenteral analgesic in Canada
- Physicians require a special license to prescribe for any indication
- Variable pharmacokinetics make dosing complex
- Regulations requiring daily witnessed ingestion by a pharmacist are restrictive.

### ***Investigational/Unapproved Uses:***

- Antitussive

### **CONTRAINDICATIONS:**

- Known hypersensitivity to methadone
- Acute respiratory depression, acute asthma attack, upper airway obstruction
- Obstetrical analgesia

### **PRECAUTIONS:**

- Drug dependence (may cause physical and psychological dependence and tolerance)
- Driving and operating machinery (may impair mental and/or physical abilities initially or when doses are changed)
- Sudden withdrawal from opioids may result in withdrawal symptoms (*See Side Effects*)
- Switching abruptly from another opioid to methadone: risk of respiratory depression
- Risk of overdose in methadone maintenance programs:
  - Overestimated tolerance and underestimated accumulation typically occur when the methadone dose is increased too early before the full effect of the current dose can be properly assessed, as steady state requires 5-7 days. This may lead to inadvertent overdose during the first two weeks of therapy or during increases in dose or addition of interacting medications
  - Clinically significant loss of tolerance to opioids may occur after 3 days without methadone; consider reducing the dose of methadone at this time to prevent overdose
  - Patients diverting part or all of their methadone doses who are then made to take the full prescribed dose in a hospital or prison setting will be at risk for overdose and death
  - Anxiety during maintenance therapy: if misdiagnosed as opioid abstinence, it will not respond to increased methadone doses

- Benzodiazepines and alcohol use during initiation of therapy is associated with an increased risk of complications including overdose
- Monitoring methadone maintenance: Random urine drug screens are used to document baseline drug use, periods of abstinence, minimize drug interactions, and assist in evaluating compliance with methadone. While routine serum methadone levels are not recommended, evidence suggests better outcomes with trough levels greater than 150-200 ng/mL (0.49-0.65 micromol/L). May be useful to confirm fast metabolizer status.
- Pain therapy in methadone maintenance patients: Tolerance will develop to the analgesic effects of methadone during longterm maintenance, therefore additional analgesics would be needed to treat pain. Supplemental doses of methadone for treatment of severe pain in methadone-maintained patients is not recommended; use another opiate.
- Acute abdomen (may obscure diagnosis or clinical course)
- Acute asthmatic attack, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, preexisting respiratory depression, hypoxia or hypercapnia (may decrease respiratory drive and increase airway resistance)
- Addison's disease (hypoadrenalism is a side effect)
- Diarrhea associated with pseudomembranous colitis or caused by poisoning until toxic material eliminated (may impede elimination of toxin)
- Elderly, debilitated, severe impairment of hepatic or renal function: reduce initial dose (decreased clearance or increased sensitivity)
- Gallbladder disease or gallstones (may cause biliary contraction)
- Head injury or increased intracranial pressure: may obscure the clinical course (sedation and papillary changes), result in increased respiratory depressant effects and elevate cerebrospinal fluid pressure (due to respiratory depression-induced carbon dioxide retention)
- Hypotensive patients (may result in severe hypotension or orthostatic hypotension)
- Hypothyroidism (increased risk of respiratory depression and prolonged CNS depression)
- Prostatic hypertrophy or urethral stricture: reduce initial dose (may cause urinary retention)

#### **PREGNANCY AND LACTATION:**

Not recommended for obstetrical analgesia. An increase in congenital defects has not been observed. Rapid withdrawal from heroin or other opiates during pregnancy carries a risk of spontaneous abortion, premature delivery and increased neonatal mortality rates. Women who use opiates during pregnancy have an increased rate of intrauterine growth restriction and intrauterine fetal death, but methadone is not associated with an increased rate of intrauterine fetal death. Compared to infants exposed to heroin in utero, infants exposed to methadone have higher birth weights, although they are still below normal. These reports have been inconsistent. Hyperbilirubinemia occurs more frequently among infants exposed to methadone in utero compared to heroin-exposed infants. Studies investigating the risk for Sudden Infant Death Syndrome (SIDS) among infants exposed to methadone in utero have had inconsistent conclusions. Use of higher doses of methadone reduced prematurity and low birth-weight, two factors associated with SIDS. Infant development scores in numerous studies are lower than controls, but remain within the normal range.

Therefore, while the use of methadone during pregnancy is associated with known risks, the benefits outweigh them. The use of methadone during pregnancy is aimed at decreasing the incidence of maternal and fetal complications which may occur during illicit heroin use. It promotes stabilization of lifestyle, improves nutrition, decreases risk for exposure to HIV and increases regular healthcare, and is preferred to opiate detoxification with its hazard of abortion in the first trimester and fetal distress due to withdrawal in the third trimester. See DOSAGE.

Opiate withdrawal occurs in 60-90% of infants born to mothers on methadone with less than one-third requiring therapy. Symptoms usually occur within 48-72 hours but may be delayed up to 7-14 days depending on the timing of the mother's last dose before delivery and the neonate's ability to metabolize the methadone. Symptoms include irritability, hyperreflexia, tremors, seizures (rare), poor feeding, excessive sucking, repeated sneezing, repeated yawning, nasal stuffiness, tachypnea, skin abrasions at pressure points, mottling, disturbed sleep, fever, diarrhea and/or high pitched crying. Recommended treatment for neonatal abstinence syndrome is supportive care in a calm environment and, depending on severity of symptoms, oral opiate therapy with gradual withdrawal.

In a series of 12 breastfeeding mothers receiving an average daily methadone dose of 43mg (range 20-80 mg), the mean milk:plasma ratio of methadone was 0.44 (range 0.13-1.19). The calculated daily infant exposure to methadone was 17.4 mcg/kg, not considered to be clinically significant. Similar low milk:plasma ratios were found in a study of eight breastfeeding mothers receiving an average daily maternal methadone dose of 80mg. Peak milk

concentrations occur 4 hours after oral dosing. The amount in breast milk is enough to prevent neonatal withdrawal in some cases but not all, since a narcotic abstinence syndrome occurred in 7 out of 12 breastfeeding infants in one study, while there have been two case reports of opiate withdrawal in infants following sudden cessation of breastfeeding.

Therefore, the dose of methadone received by the breastfeeding infant is clinically insignificant and the benefits of breastfeeding outweigh the risks of exposure. It has been recommended that by expressing the milk at four hours post dose, the mother can minimize the infant's exposure to methadone. Infants should be monitored for narcotic withdrawal or sedation.

**SIDE EFFECTS:**

With longterm therapy, common side effects progressively resolve, with the exception of constipation and sweating.

**Cardiovascular:** Hypotension, bradycardia, palpitation, faintness, peripheral edema (common, may be transient), ventricular tachycardia (cases, at very high doses), dose-dependent QT prolongation, syncope (rare), torsades de pointes (at very high doses; the mean daily methadone dose was about 400mg (range 65-1000mg) in a case series of 17 methadone patients who developed torsades; 14/17 patients had risk factors).

**CNS:** Lightheadedness, dizziness, euphoria, dysphoria, weakness, headache, insomnia and/or early awakenings, agitation, disorientation, visual disturbances, hallucinations, sedation (during initial stages or dose changes; tolerance develops to sedation).

**Dermatologic:** Sweating (common), flushing, generalized or facial pruritus without other allergic symptoms. These are due to histamine-releasing effects.

**Endocrine/Metabolic:** Weight gain (common), gynecomastia, hyperprolactinemia, hypoadrenalism, increased thyroid-hormone-binding protein, increased T4, increased T3.

**Gastrointestinal:** Nausea (common, tolerance usually develops), vomiting, anorexia, biliary tract spasm (rare), constipation (common), dry mouth.

**Genitourinary:** Urinary retention or hesitancy, antidiuretic effect, reduced libido (common, may be transient), impotence, decreased serum testosterone, irregular menstrual periods, rhabdomyolysis (in overdose).

**Hematologic:** Thrombocytopenia (reversible case in a patient with hepatitis).

**Hypersensitivity:** Pruritus, urticaria, skin rashes, edema, haemorrhagic urticaria.

**Neuromuscular:** Choreic movements, reversible spastic paraparesis (single case at a very high IV dose), myoclonus (rare).

**Ocular:** Blurred or double vision.

**Respiratory:** Respiratory depression, pulmonary edema.

**Other:** Miosis, physical dependence. Withdrawal syndrome (cardiovascular system (tachycardia, hypertension), central nervous system (mydriasis, restlessness, irritability, insomnia, craving, tremors, depression, dysphoria, emotional lability), gastrointestinal (nausea, vomiting, diarrhea), skin (piloerection, sweating), mucous membranes (rhinorrhea, lacrimation) and other (yawning, fever, myalgia). Occurs within 8-10 hours of withdrawal from heroin and peaks at 36-72 hours, subsiding after 5 days. Occurs 1-2 days after withdrawal from methadone, peaks at 4-6 days, and subsides 10-21 days after the last dose. Protracted abstinence syndrome following withdrawal from any opioid (subtle disturbances of mood and sleep, fatigue, dysphoria, irritability) can persist for weeks or up to 6 months).

**DRUG INTERACTIONS:**

Consider potential problems with both the use AND discontinuation of interacting drugs; methadone dosing may require adjustment. Methadone is a substrate of CYP3A4, 2D6, 1A2, 2C8, 2C9, 2C18, and 2C19 and an inhibitor of CYP3A4 and 2D6. Since CYP3A4 is the primary enzyme responsible for metabolism of methadone, caution should be taken with co-administration of inhibitors of CYP3A4.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Abacavir	Decreased methadone levels	Increased methadone metabolism	Caution
Alcohol (acute)	Increased risk of death in overdose	Additive	Avoid

Alcohol (chronic)	Opiate withdrawal symptoms	Increased metabolism of methadone	Caution
Anticholinergics, antidiarrheals (kaolin, pectin, belladonna alkaloids, loperamide, opium tincture, paregoric)	Increased risk of constipation	Additive	Caution
Antihypertensives	Increased risk of orthostatic hypotension	Additive	Caution
Barbiturates	Opiate withdrawal symptoms; decreased methadone levels	Increased methadone metabolism	Caution; adjust methadone dose
Carbamazepine	Opiate withdrawal symptoms; decreased methadone levels	Increased methadone metabolism	Caution; adjust methadone dose
Cimetidine	Increased methadone levels and toxicity	Decreased methadone metabolism	Caution
Ciprofloxacin	Increased methadone toxicity	Decreased methadone metabolism	Caution; adjust dose
CNS Depressants (narcotic analgesics, general anaesthetics, phenothiazines, tranquillizers, sedative-hypnotics, tricyclic antidepressants, alcohol)	Respiratory depression, hypotension, sedation, coma, increased risk of death in overdose	Additive	Caution; reduce dose of methadone
Desipramine	Increased desipramine levels and toxicity	Decreased desipramine metabolism	Caution
Dextromethorphan	Increased dextromethorphan toxicity	Decreased metabolism; additive NMDA antagonism?	Caution
Fluconazole	Increased methadone levels	Decreased methadone metabolism	Caution

Fluoxetine	Increased methadone levels	Decreased methadone metabolism	Caution (inconsistent reports)
Fluvoxamine	Increased methadone levels and toxicity	Decreased methadone metabolism	Caution; adjust methadone dose or consider citalopram or sertraline
Fusidic acid	Opiate withdrawal symptoms	Increased methadone metabolism	Caution
Ketoconazole	Increased methadone levels	Decreased methadone metabolism	Caution
Moclobemide	Enhanced effect of methadone	Decreased methadone metabolism	Caution when starting or stopping moclobemide
Monamine oxidase Inhibitors (MAOI)	CNS and respiratory depression; sympathetic stimulation	Unknown	Caution; begin with small incremental doses monitoring vital signs
Nonnucleoside reverse transcriptase inhibitors (NNRTI) (efavirenz, nevirapine)	Opiate withdrawal symptoms, decreased methadone levels	Increased methadone metabolism	Caution; may require increased methadone dose 7-10 days after starting NNRTI
Nonnucleoside reverse transcriptase inhibitors (NNRTI) (delavirdine)	Increased methadone effects	Decreased methadone metabolism	Caution (theoretical)
Nucleoside reverse transcriptase inhibitors (NRTI) (non-enteric coated didanosine, stavudine)	Decreased NRTI levels	Decreased bioavailability	Caution, monitor for virologic effect

Opioid agonist-antagonist (pentazocine, butorphanol, nalbuphine)	Opiate withdrawal symptoms	Antagonism	Avoid
Opioid antagonists (naloxone, naltrexone)	Opiate withdrawal symptoms	Antagonism	Avoid
Paroxetine	Increased methadone levels	Decreased methadone metabolism	Caution consider lower methadone dose
Phenobarbital	Opiate withdrawal symptoms; decreased methadone levels	Increased methadone metabolism	Caution, adjust dose
Phenytoin	Opiate withdrawal symptoms	Increased methadone metabolism	Caution; adjust methadone dose or consider alternative anticonvulsant
Primidone	Opiate withdrawal symptoms; decreased methadone levels	Increased methadone metabolism	Caution, adjust dose
Protease inhibitors (amprenavir, nelfinavir, ritonavir)	Opiate withdrawal symptoms; decreased methadone levels	Increased methadone metabolism	Caution (does not occur with indinavir or saquinavir)
Rifampin	Opiate withdrawal symptoms, decreased methadone levels	Increased methadone metabolism	Caution, adjust methadone dose
Risperidone	Opioid withdrawal symptoms	Increased methadone metabolism	Caution
Sertraline	Increased methadone levels	Decreased methadone metabolism	Caution
St. John's wort	Opiate withdrawal, decreased methadone levels	Increased methadone metabolism (via CYP3A4 and P-glycoprotein)	Avoid



Urinary acidifiers (ammonium chloride, ascorbic acid, potassium or sodium phosphate)	Opiate withdrawal symptoms, decreased methadone levels	Increased methadone elimination, decreased renal tubular reabsorption	Caution
Urinary alkylating agents	Increased methadone levels and effect	Decreased methadone elimination	Caution
Zidovudine	Increased zidovudine levels	Inhibition of zidovudine metabolism; inhibition of zidovudine renal clearance	Caution; monitor for zidovudine toxicity (conflicting reports)

**DOSAGE:**

Prescribed only by physicians who have received special authorization from Health Canada or the College of Physicians and Surgeons.

**Adults:**

**Detoxification of opioid dependence:**

The aim of detoxification is to have the patient drug free, by substituting methadone for the opiate and then slow withdrawal of methadone.

Outpatients: Initial dose is between 10-40 mg daily. Wait 4-6 days, then adjust dose over the next 4-6 days based on symptoms of withdrawal or intoxication. Adjust dose to control withdrawal symptoms, without respiratory depression and minimal sedation. Usual maximum dose is 50 mg daily. Once stabilized decrease the effective dose by 10% every 5 days. Duration of treatment is 7-8 weeks.

**Maintenance of opioid dependence: Methadone Maintenance Therapy (MMT)**

The goal of methadone maintenance is to relieve the withdrawal effects and craving for opiates, achieving a “blocking dose” at which the addition of other opiates fails to induce euphoria, without causing side effects. The College of Physicians and Surgeons of Ontario (Canada) Methadone Maintenance Guidelines: Initial dose 15-30 mg daily x 3 days. Increase the dose by 5-15 mg every 3-4 days. When daily dose has reached 60-80 mg increase by 5-10 mg per week. Criteria for dose increases include: 1) withdrawal signs and symptoms (*see Side Effects*); 2) no decrease in amount and/or frequency of opioid use; 3) persistent cravings for opioids; 4) failure to block euphoria of short acting opioids. Stabilization should take 2-6 weeks. Once stabilized, doses should not be sedating, cause analgesia or euphoria, i.e. patients should be able to function normally, performing mental and physical tasks without impairment. Caution: overestimated tolerance and underestimated accumulation may lead to inadvertent overdose during the first two weeks of therapy. Usual dose range 40-120mg/day when stabilized. Doses above 120 mg daily are considered high doses. Rapid metabolizers may require divided daily dosing or higher doses. For the maintenance treatment of heroin addiction, daily methadone doses of 50mg or more result in higher retention rates and fewer opioid-positive urine samples than doses <50 mg.

**Missed doses:** Clinically significant loss of tolerance to opioids may occur after **3 days** without methadone; consider reducing the dose of methadone at this time to prevent overdose. Dose can be rapidly increased over a period of days to the previous dose after tolerance to the first dose is evident. After missing methadone for **5 days** or more, begin dosing at 30 mg or less for 3 days. Then adjust relatively quickly to previous stable dose.

**Vomited doses:** Witnessed emesis <15 minutes after consumption: replace full dose. 15-30 minutes after consumption: replace 50% of dose. >30 minutes after consumption: no replacement.

**Stopping methadone maintenance:** Usually completed over several months or even one year when withdrawal is elective. Reduce dose by no more than 10% at intervals of at least one week. Discomfort may appear when the starting dose has been decreased by 30-50%. For situations of rapid withdrawal when patient privileges are removed, reduce the dose by 10% daily until discontinued. Doses <25 mg daily are more likely to result in withdrawal symptoms as it may not last the full 24 hours. At that point withdraw no more than 5 mg/week.

**Pain management:**

Only those physicians experienced with the use of methadone and its pharmacokinetics should initiate methadone. To avoid oversedation, generally not recommended for analgesia in opioid-naïve patients. **For breakthrough pain,** use a short-acting opioid.

**Severe pain in cancer patients:**

Oral: Usual starting dose 5-10 mg every 6-8 hours. Monitor carefully to avoid accumulation of drug and respiratory depression.

**Chronic nonmalignant pain:**

**Oral: Opioid-naïve or patients taking codeine:** Start at 2.5 mg every 8 hours.

**Patients already taking oxycodone or up to 200mg/day oral morphine:** Start at 5 mg orally every 8 hours. Increase by 5 mg every 8 hours every 5-7 days. Titrate until adequate pain relief or side effects (sedation). Look for graded analgesic response to indicated opioid-responsive pain. Assess weekly during titration, every 1-2 months during maintenance.

**Morphine >200mg orally daily or high-dose opioid:** Use equianalgesic dose (see below).

**Morphine >500mg orally daily or morphine equivalents:** Decrease the opioid by 1/3 every 5 days. Introduce 1/3 equianalgesic dose of methadone every 5 days (see below). The entire conversion should take 15 days.

**Equianalgesic doses (previous chronic dosing with an opioid):**

When determining equianalgesic dose consider such factors as drug interactions, age, family support for outpatients, pharmacokinetic variability and other risks of toxicity. Methadone has incomplete cross-tolerance to other opioid analgesics; therefore use extreme caution when considering conversion to equianalgesic doses.

2mg oral methadone = 30mg oral morphine = 10mg morphine IM/SC = 8mg oral hydromorphone = 2mg hydromorphone IM/SC = 15mg oral oxycodone.

Numerous different equianalgesic charts and conversion schedules for inpatient and outpatients have been used for management of cancer and noncancer pain. Length of the switch varies from 1-32 days, with outpatient switch taking longer. Some experts recommend a minimum overlap period of 3 days for inpatients and 5-6 days in the home, the latter only with competent and reliable patient and significant other. Conversion ratios may become more inaccurate with larger opioid doses. Some equivalence ratios are inversely correlated to dose of morphine.

**Intractable cough associated with terminal lung cancer: Oral:** 1-2 mg every 4-6 hours, reduced to twice daily with prolonged use.

**Elderly:** Reduce initial dose.

**Hepatic impairment:** Reduce initial dose in severe disease.

**Renal impairment:** For Cl<sub>cr</sub> <10mL/min, give 50% of normal dose or avoid.

**Debilitation, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture:** Reduce initial dose.

**Pregnancy:**

During the third trimester of pregnancy increased volume of distribution and placental metabolism may result in need for increased doses. A prospective study found higher doses of methadone during the third trimester of pregnancy associated with increased head circumference mediated by improved growth and prolonged gestation. Use lowest effective dose.

**Children:** Not approved for use in pediatrics.

Analgesia: Oral: 0.1 mg/kg/dose every 4 hours for 2-3 doses then every 6-12 hours. Maximum dose: 10 mg/dose. Iatrogenic narcotic dependence: 0.05-0.1 mg/kg/dose every 6 hours; increase by 0.05 mg/kg/dose until withdrawal symptoms are controlled; after 24-48 hours lengthen interval to every 12-24 hours. To taper decrease by 0.05 mg/kg/day. Taper at a slower rate if withdrawal symptoms occur.

**NURSING IMPLICATIONS:**

Administer oral drug without regard to food. Ingestion should be witnessed by the nurse.

Common side effects are nausea, constipation, sweating, drowsiness and dry mouth. Dangerous side effects of methadone include respiratory depression, dizziness and rarely ventricular arrhythmias and torsades de pointes. Supervise ambulation. Encourage fluids and dietary fibre. Encourage good oral hygiene, particularly with chronic therapy. Urinary retention may also occur. If the patient has problems with vomiting when taking the drug, encourage him or her to take the drug in small sips.

This drug has a long half-life and may accumulate with prolonged dosing. Notify physician if patient is drowsy or has respiratory depression before administering the dose. Patients should be monitored for drowsiness and respiratory depression at least twice daily.

The short-term therapeutic benefits in the maintenance of opioid dependence include decreased drug craving and prevention of opiate withdrawal. Longterm therapeutic benefits in this setting include decreasing the use of illicit drugs, reducing needle sharing, reducing criminality and improved social reintegration.

Methadone is indicated for the management of chronic pain in patients exhibiting opioid toxicity including myoclonus, hallucinations, delirium and hyperalgesia (loss of previous pain control or extreme sensitivity of the skin to touch). Switching to methadone may provide pain control without the previous side effects.

Abrupt withdrawal may lead to opioid withdrawal syndrome. Do not discontinue suddenly.

Store oral diluted solutions in the refrigerator. When mixed with compatible juices, methadone is usually stable for 14 days in the refrigerator (7 days for Allen's Apple Juice).

**PATIENT INSTRUCTIONS:**

Methadone (METH-a-done) is used to treat severe pain.

Methadone is used as a substitute for heroin or other drugs such as morphine for controlling withdrawal symptoms. With each dose of methadone, narcotic withdrawal and craving is suppressed for 24-36 hours. If you have a history of heroin use and you take heroin concurrently with methadone, the euphoric effect of the heroin may be decreased or eliminated by the methadone. If this happens and you increase your heroin dose you may overdose. Overdose with heroin has resulted in death.

Methadone helps to stabilize physical and emotional symptoms of withdrawal from the opioid to allow for counseling and lifestyle changes needed for recovery and allowing for abstinence of narcotic use. During maintenance you may experience improved health, alteration of lifestyle, and improvement of social and family circumstances.

Take this medication with or without food.

Take this medication exactly as prescribed. Measure the dose carefully. Do not miss taking your methadone on a daily basis. Talk to your physician before stopping this medication; gradual dose reduction may be needed to avoid withdrawal symptoms. For the treatment of heroin addiction, methadone can be taken safely for many years.

If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and continue with your regular schedule. If you have missed more than two doses, check with your doctor before taking further doses. If you have problems with vomiting after taking your dose of methadone, try consuming the methadone slowly in small sips.

Contact your physician or seek medical attention immediately if your pain becomes worse or if you experience fast or slow heartbeat, dizziness, fainting, trouble breathing, hives, skin rash or itching, severe confusion, or hallucinations.

Tell your physician if you have the following side effects: drowsiness, dizziness, weakness, headache, dry mouth, nausea, vomiting, constipation, excessive sweating, facial flushing (redness), sleep disturbances, change in menstruation, muscle and bone aches, fluid retention, weight changes. For dry mouth use sugarless gum or candy, ice or saliva substitute for relief. Check with your dentist if dry mouth continues for more than 2 weeks. Methadone could cause constipation. You can treat and prevent this by increasing fluid and fiber intake and using stool softeners. Methadone may cause decreased libido. Fertility may improve during stabilization on methadone, therefore consider family planning.

If you suddenly stop methadone therapy you may experience symptoms of withdrawal including insomnia, runny nose, yawning, dilated pupils, goose pimples, tremors, sweating, chills, anxiety, agitation, abdominal pain, diarrhea, and musculoskeletal pain. Contact your physician if you are experiencing any of these symptoms.

Be careful if driving a car or using hazardous machinery because methadone could make you dizzy or drowsy. Avoid alcohol or sedating medications such as sleeping pills, muscle relaxants, sedatives or cold and allergy medicine, unless approved or prescribed by your doctor. Prescription, nonprescription, herbal and street drugs may change the way methadone works in your body. Check with your physician or pharmacist before taking any medications while on methadone.

Ensure that every physician or dentist who treats you is aware that you are taking methadone.

If you are pregnant, intend to become pregnant, or are breastfeeding, talk to your doctor about the benefits and risks of taking methadone. If you take methadone while you are pregnant, after your baby is born there is a high chance that your child will experience narcotic withdrawal during the first 2-3 days after birth. Talk to your physician about what to watch out for in your baby. Small amounts of methadone are present in breast milk, and high methadone doses may cause dependence in the nursing baby. Suddenly stopping breastfeeding may result in a withdrawal syndrome in your child (this has been reported rarely). Talk to your doctor before stopping breastfeeding.

Store in the refrigerator out of the reach of children, preferably locked up. Do not freeze. Accidental ingestion of methadone by a child could cause death.

#### **PRESENTATION:**

Oral solution: 1 mg/mL (as racemic HCl salt) 100 and 250 mL bottles; 10 mg/mL (as HCl salt) 100 mL and 250 mL bottles. Store at room temperature, keep tightly closed, protect from light and freezing.

Tablets: 1, 5, 10 and 25 mg (as racemic HCl salt).

Powder: 1, 25, 100 g (as racemic HCl salt) Powder should be stored in a labeled, airtight, light protecting container.

Manufactured: other solutions, suppositories.

#### **Dispensing**

For detoxification and maintenance therapy but not pain therapy, solution must be dispensed in a vehicle not lending itself to injection, e.g. not water. Note: "In British Columbia, methadone for maintenance should always be dispensed to patients in a concentration of 1 mg/mL. If the dose is 50 mg, the patient receives 50 mL; if the dose is 80 mg, 80 mL is dispensed. The practice of dispensing as a standard volume (e.g. all doses dispensed as a volume of 100 mL) is not acceptable" in British Columbia.

Diluents compatible with Metadol solution include Grape flavoured Kool-Aid, Orange flavoured Tang, Allen's Apple juice, Crystal Light Tangerine-Grapefruit flavoured, Crystal Light Lemonade flavoured. {Pharmascience 2003} Stable refrigerated for 14 days (7 days for Allen's Apple Juice). For more detailed stability information of methadone solutions, refer to the BC Methadone Maintenance Treatment Program, Information for Pharmacists, revised May 2005, available from: [www.bcpharmacists.org](http://www.bcpharmacists.org)