PURPOSE

To assure the proper use and dosing of methadone for the management of chronic pain and the minimization of risk for serious side effects.

POLICY

All DOP Primary Care Providers are to be familiar with these guidelines. All prescribing of methadone in the DOP will be supervised by specifically designated Clinical Pharmacists trained in the management of methadone. All use of methadone in non-terminally ill patients must be approved by Utilization Review.

PROCEDURE

1) Methadone is a long half-life narcotic for treatment of pain approved by the FDA.
2) Advantages:
   a) Highly effective
   b) Very low cost
   c) Convenient dosing schedule
   d) Very flexible dosing
   e) Low level of stimulation ("high")
   f) Relatively low side effects
   g) True long half life opioid (does not require sustain release)
      i) Available in liquid formulations
      ii) Can be crushed
   h) NMDA receptor antagonist
      i) May be effective against neuropathic pain
      ii) Prevention of opioid tolerance
      iii) Potentiation of opioid effects
3) Disadvantages:
   a) Variable and very long half life
   b) Respiratory depressant effects last much longer then pain control
   c) Minimum of 5 days to reach steady state
   d) Numerous drug interactions
   e) Multi-compartment pharmacokinetics
   f) QT prolongation on EKG
   g) Synthetic opioid, not detected in most urine drug screens

4) Pharmacokinetics

	Parameter	Average	Range
a)	Bioavailability	70-80%	36-100%
b)	Tmax	2.5 – 4.0 hours	1.0 – 5.0 hours
c)	Protein binding	87%	81-97%
d)	Half-life	20 – 35 hours	5 – 130 hours
e)	Liver metabolized		

i) No active metabolites
ii) Fecal excretion
iii) No renal adjustment needed

5) Two Compartment Modeling
   a) Half life in central compartment is relatively short (3 – 5 hours) and is the reason for the short analgesic effect with "acute" dosing
   b) Long chronic half life is due to the fact that part of each dose enters a secondary compartment and forms a long lasting deposition which is in equilibrium with the central compartment. This takes on average 5 -10 days to reach a steady state after each dosing change.

6) Drug interactions
   a) N-demethylation by 3A4, 2B6, 2C19, 2C9, 2D6
   b) Contraindicated: Opioid antagonists, mixed, partial agonists
   c) Use with caution
      i) Enzyme inducers
         (1) may precipitate withdrawal symptoms or reduce pain control
         (2) examples: rifampin, phenytoin, phenobarital, carbamazepine, antiretrovirals
         (3) May require methadone dose adjustment particularly if added or **stopped** while on methadone
      ii) Enzyme inhibitors
         (1) May increase side effects or precipitate overdose
         (2) Examples: azole antifungals, fluconazole, omeprazole, macrolides, SSRIs, variconazole
         (3) Not necessarily contraindicated but may require a reduction in methadone dose (or increase if discontinued)

7) QT prolongation
   a) Rare; only about 60 reports to FDA in the past 30+ years
   b) Routine EKG screening not indicated
   c) Consider doing EKG if:
      i) Structural heart disease
      ii) LV dysfunction
      iii) Hypokalemia
      iv) Liver dysfunction
      v) 3A4 drug interactions
      vi) Multiple QTc prolonging drugs
      vii) Family/personal history of long QT
      viii) Family history of sudden death
      ix) High dose of methadone
   d) Examples of QT prolonging drugs (not a complete listing):
      i) Class I & III antiarrhytmics
         (1) amiodarone
         (2) disopyramide
         (3) procainamide
         (4) quinidine
         (5) sotalol
      ii) Some neuroleptics,
         (1) haloperidol
         (2) thioridazine

iii) Macrolides
  (1) clarithromycin
  (2) erythromycin
iv) Tricyclic Antidepressants(TCAs)

8) Starting methadone in narcotic naïve including those taking only short acting preparations
   a) 2.5 – 10 mgs PO qhs – bid
      i) Use lower doses if:
         (1) > 65 yo
         (2) Weight < 150
         (3) Comorbid conditions particularly pulmonary disease
         (4) Unable to closely monitor for 5 – 7 days after initiation or change in dose
         (5) Taking < 20 – 30 mgs per day of morphine equivalent dose of short acting narcotics
         (6) On enzyme inhibiting drugs (see below)
   b) If needed, titrate up dose every 7 – 14 days, no sooner. Titration can be done by:
      i) Increasing size of dose (indicated if pain control inadequate through out dosing interval)
      ii) Increasing frequency of dosing to q8h (indicated if pain control inadequate primarily towards the end of dosing interval); more frequent dosing should be avoided
   c) If needed may use a short acting narcotic or non-narcotic analgesic for breakthrough/uncontrolled pain while titrating methadone and/or while on chronic stable methadone therapy i.e.:
      i) Hydrocodone
      ii) Oxycodone, immediate release
      iii) Morphine, immediate release
      iv) NSAIDs
      v) Tramadol
      vi) Acetaminophen
   d) Watch for signs of overdosing 3 to 5 days after dosage changes: over sedation, confusion, etc.
9) Converting from other opioids
   a) DO NOT USE ACUTE DOSING CONVERSION CHARTS
   b) Use two or three different chronic conversion (see below) calculations to establish a range for the total daily dose of methadone (consult Central Pharmacy)
   c) Divide the above total daily dose by 2 or 3 and dose every 12 or 8 hours respectively
   d) Use low end of range for high risk patients
   e) High risk factors
      i) Age >65
      ii) Liver disease
      iii) Very high doses
      iv) Psychiatric disorders
      v) Unable to monitor for 5 – 7 days (particularly days 3 – 5)
   f) Adjust dose no sooner then 7 days
   g) Use short acting narcotics for break through pain
   h) May need to taper present long acting preparation over first two to three days of methadone dosing
      i) Day 1: Replace 1/3 of opioid dose with methadone on a bid/tid schedule
      ii) Day 2: Replace another 1/3 of opioid dose
      iii) Day 3: Replace all of opioid with methadone
10) Chronic conversion charts: based on **oral** morphine total daily dose [MTDD] including chronic long acting narcotic dose plus average daily amount of breakthrough medicine.

a) If taking an opioid other then morphine, use standard opioid conversation chart to determine morphine equivalent dose.

Opioid	Oral(mg)	Parenteral(mg)
Morphine	30	10
Codeine	200	130
Hydrocodone	30	-
Hydromorphone	7.5	1.5
Levorphanol	4 (acute) 2 (chronic)	2 (acute) 1 (chronic)
Meperidine	300	75
Oxycodone	20	-
The microgram/hour dose of transdermal fentanyl is approximately equal to one-half the milligram/day dose of oral morphine (e.g., 100 mcg/hr transdermal fentanyl = 200 mg/day oral morphine)		

b) Chronic narcotic to methadone conversion charts
   i) Friedman
      (1) < 1000 mg morphine MTDD and < 65 y/o = 10:1 (i.e. 10 mg morphine: 1 mg methadone)
      (2) 1000 – 2000 MTDD or > 65 y/o = 20:1 morphine total daily dose: methadone total daily dose
   ii) End of Life / Palliative Education Resource Center, Equianalgesic dose (ratio of oral morphine to oral methadone*)
      (1) < 100 mg - 3:1 (i.e. 3 mg morphine: 1 mg methadone)
      (2) 101-300 mg - 5:1
      (3) 301-600 mg - 10:1
      (4) 601-800 mg - 12:1
      (5) 801-1000 mg - 15:1
      (6) > 1000 mg - 20:1
      *** Initial dose is 50-75% of the above dose**
   iii) FDA recommendation (package insert) = percent of total daily **oral** morphine dose
      (1) < 100 mg - 20-30%
      (2) 101-300 mg - 10-20%
      (3) 301-600 mg - 8-12%
      (4) 601-1000 mg - 5-10%
      (5) > 1000 mg - < 5%

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9/30/10

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