Substance Abuse and Pregnant Women

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Methadone: The Basics: How It Works
GOALS FOR PHARMACOTHERAPY

• Prevention or reduction of withdrawal symptoms
• Prevention or reduction of drug craving
• Prevention of relapse to use of addictive drug
• Restoration to or toward normalcy of any physiological function disrupted by drug abuse

Source: MJ Kreek, Rationale for Maintenance Pharmacotherapy of Opiate Dependence, 1992
Normal Function and Women

- Addiction to opioids severely disrupts the menstrual cycle.
- One reason for addicted women coming into treatment later in pregnancy.
- Methadone normalizes the menstrual cycle
- Patients need to be aware of normalization and use appropriate means to prevent unwanted conception.
PROFILE FOR POTENTIAL PSYCHOTHERAPEUTIC AGENT

• Effective after oral administration
• Long biological half-life (>24 hours)
• Minimal side effects during chronic administration
• Safe, no true toxic or serious adverse effects
• Efficacious for a substantial % of persons with the disorder

Source: MJ Kreek, Rationale for Maintenance Pharmacotherapy of Opiate Dependence, 1992
Development of Tolerance/Dependence

...loss of on/off condition

— with continued and repeated use

Tolerance develops (↑ dose for desired effect)

Physical dependence develops (Withdrawal syndrome on abrupt cessation of the drug)

Leading to:
Tolerant/Dependent Drug States

Drug Effect Scale

Time

“Loaded”

“High”

Normal Range
“Comfort Zone”

“Sick”
Heroin Simulated 24 Hr. Dose/Response
With established heroin tolerance/dependence

- "Loaded"
- "High"
- "Abnormal Normality"
- Normal Range "Comfort Zone"
- Subjective w/d "Sick"
- Objective w/d

Dose Response

Time

0 hrs. 24 hrs.
Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient

“Loaded”
“High”

“Abnormal Normality”

Normal Range
“Comfort Zone”

Subjective w/d
“Sick”
Objective w/d

Dose Response

0 hrs. 24 hrs.

Time
Impact of Maintenance Treatment

- Reduction death rates (Grondblah, ‘90)
- Reduction IVDU (Ball & Ross, ‘91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion (Bourne, ‘88; Novick ‘90,; Metzger ‘93)
- Reduction relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function
Issues in Maintenance:

HOW MUCH?

&

HOW LONG?
How Much?

ENOUGH!!!
How Long Does OAT Last?

Long Enough!!

...As long as patient desires and benefits from continued treatment
SAFE INDUCTION TECHNIQUES
Patients are 6.7 times more likely to die during induction than untreated heroin addicts (Caplehorn & Drummer, 1999).

42% of drug-related deaths occurred during the first week of OMT (Zador & Sunjic, 2000).

10 OMT deaths are reported — All 10 had been in treatment less than 7 days (Drummer, Opeskin, Syrjanen & Cordner, 1992).
## Initial Dose

<table>
<thead>
<tr>
<th>Degree of Tolerance</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Tolerant</td>
<td>10 mg +/- 5</td>
</tr>
<tr>
<td>Unknown Tolerance</td>
<td>20 mg +/- 5</td>
</tr>
<tr>
<td>Known Tolerance</td>
<td>20-40 mg</td>
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</tbody>
</table>
Early Induction

Early dose adjustments to reach the “Therapeutic Window” as
determined by established opioid tolerance.

- The “Comfort Zone” –

Increase dose until pt. comfortable during methadone peak levels (3-5 hours after dose) then;

Hold dose for 3-5 days to reach steady-state before further dose adjustments.

**REMEMBER STEADY-STATE PHARMACOLOGY!**
Early Induction- 2

- Effect of a dose IS NOT determined by clinical presentation at 24 hours..

- Effect of a given dose is based on status at 3-8 hrs.

The patient doing well at 3-5 hours may not need a dose increase, unless showing s/s withdrawal.
Early Induction- 3

- ANY SIGN OR SYMPTOM OF OVER-MEDICATION DURING EARLY INDUCTION REQUIRES A DOSE REDUCTION!

Beware the subtle s/s of overmedication; feeling good, extra energy, staying awake to work, etc. (“Abnormal Normality”)

Patients may need more time, not more meds!
Induction Simulation – Low Dose/Low Tolerance with failure to reduce dose on day 2 or 3

Dose remains constant to steady-state in toxic range
Induction Simulation – Low Dose/Low Tolerance with reduced dose on day 3 & 4

Intoxication, Potential OD

Therapeutic Window

Time in Days = Dose Reduction

Dose Reduction

0 50 100 150 200 250 300

ng/ml

mg/day
Clinical Pearls

Very severe withdrawal s/s does not mean very high tolerance or the need for higher doses of methadone.

Consider use of instant opiate screens on admission with 2000 ng cut-off

Document si/sx withdrawal with at least 2 objective signs.

Document daily assessment during induction including basis for decisions to increase dose.
MAINTENANCE: PRINCIPLES OF ADEQUATE DOSING
OPTIMAL RESPONSE FROM OPIOID AGONIST IN MAINTENANCE TREATMENT

• Prevention of onset of withdrawal syndrome for 24 hours or more
• Reduction or elimination of drug hunger or craving
• “Blockade” of euphoric effects of illicit self-administered opioids

Kreek, 1987 – title change by Payte, 2001
ADEQUACY OF DOSE IS BASED ON 2 FACTORS:

• The amount of medication (size of dose)

  And

• Frequency of dosing; the inter-dose interval (24, 12, 8, hrs., etc.)
INDIVIDUALIZED!

ADEQUATE DOSE

... based on clinical response
How much is enough?

The amount required to produce the *optimal response* for the appropriate duration of time, with an allowance for a margin of effectiveness and safety.
Optimal Vs. Desired Response

The clinician and the patient must speak the same language to ensure realistic expectations and goals of OAT. A pattern of dose escalation in pursuit of the elusive state of “abnormal normality” must be recognized by the patient and the clinician.
Maximum Dose?

• Arbitrary dose ceilings have no foundation in science or clinical practice.

• Dose caps ensure inadequate treatment for a significant proportion of patients.

• Dose caps are not supported by CSAT, AATOD, NAMA, ASAM, CMG, or any credible entity.
METHADONE BLOOD LEVELS

Why? When? Where?
FIG. 1. Mean (± SEM) plasma methadone concentration-time profile during a single 24-hour interdosing interval in 18 methadone patients.
total mood disturbance

Dyer & Associates
Serum Methadone Levels

• Define Peak to Trough ratio, the rate of decline or metabolism
• Define the optimum dosing interval to maximize benefits of OMT
• Clinical Picture / Dose Incongruities
• Suspected Drug Interactions
• Justification of “unusual” dose levels/schedules
• Monitor effectiveness of divided dose schedules
Interpretation of Serum Methadone Levels

- Peak or trough Levels alone are of negligible clinical utility in determining adequacy of a given dose

**Dose adequacy is determined clinically!**

Optimum levels for cross-tolerance (“Blockade”) are thought to be 400 ng/ml or more

Peak/Trough Ratio ideally less than 2, 700/400=1.75, values > 2 suggest rapid metabolism, 800/200=4

**Rate of change!**
My dose isn’t “holding” me

- Environment?
- Stressors?
- Alcohol?
- Other drugs/medications?
- Vitamins? (especially C)
- Urinary pH?
- Clinically adjust methadone dose
- Methadone blood levels?
“Not Holding” Strategies

- Cognitive, Behavioral Interventions
- Increased contact, counseling, therapy
- Alter urinary pH?
- Is patient fixing? - Raise dose
- Split Dose?
Cytochrome P-450 Enzyme Activity
Drug Interactions - Methadone

• Induction
  • Rifampin
  • Phenytoin
  • Ethyl Alcohol
  • Barbiturates
  • Carbamazepine
  • Nevirapine (Viramune)
Applications of preceding

Patient c/o waking up sick daily but is sedated 3-6 hrs. after dose:

Dose increase will not make the dose last longer, just increase the fluctuation between over and under medication.

Increase frequency not dose!
Rapid Metabolizer - High Single and Split Dose Simulation

- High
- Normal
- Sick

Hours

ng / ml

Single
High Single
Split Dose
Minimum
'Normal' Ceiling
Pregnancy Case Study @ 6 mo.
“ I wake up sick & my baby moves a lot!”

![Graph showing pregnancy case study with normal and sick conditions at 6 months.](image)
Split Dose Induction
(For patients feeling OK through the day but getting sick by bedtime & worse by morning)

• Day 1: 100% of current dose, observed, & 50% of dose to take in 12 hours

• Day 2 and beyond: 50% of dose q 12 h

Note: Poor results from starting with half the usual dose on day 1
Split Dose Induction
(For patients sedated at 3-4 hours after single dose)

• Day 1: 60% of current dose observed
  50% of current dose to take in 12 hrs.

• Day 2 and beyond: 50% of dose q 12 h
  (titrated up or down as needed).

**Note:** On day 1 some patients will do better
with 60% for 2nd dose (120% of usual daily
dose, 1st day only)
Evidence-Based Practices: Elements to Maximize OAT Outcomes

• Adequate Methadone Dose
• Availability of counseling
• Maintenance versus abstinence/detoxification program orientation
• Contingency management with focus on positive and immediate reinforcement/rewards

Source: Opioid Agonist Therapy Monitoring System (OMS) Willenbring et al. 2003
Methadone and Pregnancy

- Effect of untreated opioid addiction or detoxification:
  - Increased 1st trimester spontaneous abortion
  - Increased 3rd trimester premature labor
  - Low birth weight
  - NAS
  - Other problems
Methadone and Pregnancy

- There is no evidence that higher doses are harmful to the fetus.
- The neonate has a high probability of having NAS (Neonatal Abstinence Syndrome).
- Delivery should be arranged for a hospital where the neonate can be appropriately managed for NAS, if necessary.
Questions?