Challenges of Helping People Undergoing MMT Manage Pain When Hospitalized

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What's the story of methadone?
History of Methadone

- 1st synthesized in Germany in 1930’s
- Searching for analgesia + spasmolytic medication
- Eli Lilly purchased rights for $1.00
- Lilly product methadone (Dolophine™ “dolor” & “fin”)
- Approved by FDA in 1947
- AMA assigned generic name methadone
- Treat painful symptoms of heroin withdrawal

Pharmacology

- Racemic mix with 2 Components:
  - Potent synthetic mu agonist opioid
  - NMDA receptor antagonist
- 80 - 95% bioavailability orally
- 6-12 hr analgesia duration after steady state
- Pharmacologically active portion 12% - variable
- No active metabolites
  - no dose adjustment needed with renal failure

Pharmacokinetics

- Highly lipophilic
- Quick distribution to:
  - brain muscles liver gut lungs
- Binds readily to plasma proteins
- Plasma concentration 2.5 to 4 hrs after ingestion
- Between doses
  - plasma concentrations are maintained by tissue reservoir
Half Life

- Extended terminal half-life
- Up to 190 hours
- Risk increased for
  - sedation
  - respiratory depression
- Titration needs to be slow
- Elimination half-life at steady state
  - range 4 - 91 hrs
  - average 24 - 36 hrs

Steady-state Serum Methadone Levels

- SML – elimination is balanced with amount of methadone remaining in body
- Time required to achieve is ~ 4 to 5 days
- Rule of thumb:
  - ½ daily dose remains in body
  - this is added to next daily dose
  - SML consistently rises – caution for excess
- After each dose – SML peaks in ~ 3–4 hrs
- Individual responses differ physiologically

Metabolism - Elimination

- Metabolism is primarily hepatic
- Significant fecal elimination
- Urine pH < 6 enhances renal excretion
- Biphasic elimination
Unique Characteristics
- Rapid GI absorption
- Long duration
- Good tolerance profile
- Low need for escalation
- Only long acting opioid w/multiple routes
- Inhibits norepinephrine/serotonin reuptake
- Potential activity in neuropathic pain

Potency Influences
- Genetics
- Inter-individual variation
- Intra-individual variation in opioid tolerance
  - dependent upon dosing hx of other opioids
- External stimuli
- Accumulation with repeated doses

Safety Profile
- Favorable when properly prescribed & used
- Among addiction treatment deaths
  - Largest proportion during induction phase
- Deaths during later phases
  - other substances identified on post mortem
  - additive/ synergistic effects = lethality
  - poison cocktail (mx psychotropic meds)
  - forensic challenge (methadone vs methadone +)
Positive Factors

- Effective analgesia for severe pain
- mgm – mgm more potent than morphine
- Highly lipophilic
- Low cost
- Multiple routes of administration
- Bioavailability nearly 3 x morphine

Opioid Addiction
Addiction

“A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.”

(ASAM, APS, AAPM, 2001)

Co-morbidity Pain & Addiction

- Pain of any type or duration is reported by 80% of MMTP pts & 78% of inpatients.
- Chronic severe pain is experienced by 37% of MMTP pts & 24% of inpatients.
- Among those with chronic severe pain, 65% of MMTP pts & 48% of inpatients reported high levels of pain-related interference in px & psychosocial functioning.

(Rosenblum et al, 2003)
Methadone Maintenance Treatment

- Methadone Maintenance Treatment (MMT)
- Opioid Agonist Therapy (OAT)

History of MMT

- Response to post WWII heroin epidemic
- 1949 US PHH found it most effective for withdrawing addicted people from heroin
- 1964 research project – MMT
- 1965 used only for in-patient treatment
- 1966 outpatient clinics
- 1960's Federal regulations restricted use
- 1999- Notice of Proposed Rulemaking
  - Methadone as a clinical tool
  - Programs accredited with QA guidelines

Who is involved?

- 1999 - ~ 20% of 810,000 heroin IVDA
  155,000 methadone tx
  (American Methadone Treatment Association, 1999)

- 2005 - ~ 235,836 methadone tx
  - 90,058 (40%) Maintenance only
  - 138,764 (59%) Maintenance & detox
  (DASIS Report, 2006)
How it works

- Heroin
  - Release of excess dopamine
  - Results in need to continuously occupy opioid receptor in brain
- Methadone
  - Occupies the opioid receptor
  - Stabilizing effect
  - Suppresses withdrawal x 24 – 36 hrs

(ONDCP, 2000)

Benefits of MMT

- Clinically effective for opioid addiction
  - Improved health
  - Increased productivity
- Clinically effective for infection control
- Cost effective (~ $13/ day)
- Reduction in criminal behavior
- Reduction in opioid related deaths
- Improved family relations & QOL
- Improved pregnancy outcomes

Co-morbid Opioid Addiction and Acute Pain
Pain and Opioid Dependence

- People with opioid addiction have "an abnormally low tolerance for painful stimuli." (Martin & Inglis, 1965)

- Opioids activate locus coeruleus & amygdala
  - analgesia
  - reward

Influences of Co-morbidity

- Acute pain – reduces the euphorogenic qualities of opioids

- Addiction – tends to increase painful experiences

Prevalence of Opioid Addiction

- General Population: 3 - 18%
- Chronic Pain: 3.2 - 18%
- Hospitalized Population: 20 - 26%
- Trauma Population: 40 - 62%

Acute Pain in Patients Receiving MMT

- General population of those on MMT
- Chronic pain
- Acute medical conditions
- Post-operatively
- Acute trauma

Compare

- **Prevalence of Opioid Addiction**
  - General Population: 3 - 18%
  - Chronic Pain: 3.2 - 18%
  - Hospitalized Population: 20 - 26%
  - Trauma Population: 40 - 62%

- **Acute Pain in Pts Receiving MMT**
  - General population
  - Chronic pain
  - Acute medical conditions
  - Post-operatively
  - Acute trauma
Why Should We Care?

- Ethical responsibility
- Increasing prevalence

Characteristics:
- Pain at least at same rate as others
- High incidence of trauma and chronic illness
- Aging sub-population
- Challenging pain control

Managing Acute Pain in Patients Receiving MMT
Barriers

- Myths
- Misunderstandings
- Fears
- Lack of knowledge

Common Myths

- Maintenance opioid agonist = analgesia
- Opioids for acute pain = relapse
- MMT + opioid analgesia = respiratory & CNS depression
- Pain reports/complaints = manipulation & drug seeking
- And:
  - Methadone blocks analgesic effect of opioids

Maintenance opioid agonist ≠ adequate analgesia

- Analgesic properties duration ~ 6 - 8 hrs
- Tolerance to maintenance methadone
- Cross-tolerance to morphine
  - Need higher doses
  - Need more frequent doses
- Opioid-induced hyperalgesia
**Opioids for Acute Pain ≠ Relapse**

- No evidence of relapse when opioids are used in presence of acute pain (Kantor et al, 1980; Manfredi et al, 2001)
- Theoretically greater risk of relapse with unrelieved pain
- Anecdotal experiences

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**MMT + Opioid Analgesia ≠ Respiratory & CNS Depression**

- No clinical or empirical documentation of this risk
- Tolerance to Respiratory & CNS depressing effects well documented
- Acute pain natural antagonist

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**Pain Reports/Complaints ≠ Manipulation & “Drug Seeking”**

- HCP “concern”
- Acute pain may be more easily substantiated
- Goal of tolerable comfort level
  - “Pseudoaddiction”
  - “Therapeutic dependence”

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HCP Barriers

- Opiophobia
- "Addict" vs "Recovery"
- Fear of intensifying or relapsing addiction
- Legalities
- Personal cultural beliefs
- Misunderstandings
  - re: methadone & MMT

Common Prescribing Problems

- Advise to d/c methadone pre hospitalization
- Lowering methadone dose while in-patient
- Increasing methadone dose while in-pt
- Not prescribing "additional" analgesia
- Inadequate prescription of opioids
- Inappropriate use of opioid antagonist

(Limeca, et al, 2000)

Lack of Knowledge

- Pain Management
  - Multi modal analgesia
  - Opioid management
  - Methadone pharmacokinetics/dynamics
- Addictionology
- Pain management in people in MMT
Preconceived Notions

- “Addicts”
- “Narcotics”
- “Drug seeking”
- Methadone

Patient Barriers

- Misunderstandings
- Fears
- Reluctance to fully disclose recent use
- Tolerance and cross tolerance
- Hyperalgesia

Misunderstandings

- “I can’t take narcotics because then I will start using again”
- “I can’t take the methadone because the hydromorphone won’t work”
Fears

- Fear of relapsing
- Fear of un-relieved pain
- “No one knows”
- Stigma

Patient Privacy Concerns

- HIPPA
- “No one knows”

Pharmacokinetic and Pharmacodynamic Issues

- Tolerance and cross tolerance
- Hyeralgesia
Caring for Patients Undergoing MMT Who Are Hospitalized

Multidisciplinary Approach
- MMT Team
- Physicians
- Pain specialists
- Care Nurses
- Pharmacists
- Non-pharm - complementary providers
- Behavioral health

Overcoming Barriers
- Making sense of the data
- Dispelling myths
- Education
Making Sense of the Data

- Pain threshold ("when pain 1st perceived")
- Pain tolerance (when pain stimuli no longer tolerated)
- Characteristics of people living with addiction
- Conflicting data
  - Different comparison groups
  - Different stimuli and induction of pain (cold vs electric)
  - Trough vs peak plasma levels
  - Different measurement methods
  - Sample size

(Doverty, et al, 2001)

Dispelling Myths

- Pts with MMT are generally hyperalgesic
- Cross-tolerant to antinociceptive effects of morphine common

(Education)

- Dispelling myths
- Different pain tolerance at trough vs peak levels
- Pts with MMT are generally hyperalgesic
- Cross-tolerant to antinociceptive effects of morphine common

(Doverty, et al, 2001a & 2001b)
Methadone Availability

- Formulary availability
- Patient route availability
- Thinking outside the box

Product Availability

- Oral
  - solid tablet
  - diskette (rapidly dissolving wafer)
  - pre-mixed liquid
  - all are bioequivalent to each other
- Transmucosal  (suppositories (Bruera, et al, 1995))
- IV
- SC  (some local toxicity reported (Bruera, et al, 1991))
- Epidural or Intrathecal
- Sublingual  (Hagen, et al, 2006)

Drug–Drug Interactions

- Some Rx that decrease methadone levels
  - rifampin
  - phenytoin
  - carbamazepine
  - risperidone
  - nevirapine
  - phenobarbital
  - many antiretrovirals

- Some Rx that increase methadone levels
  - amitriptyline
  - ciprofloxin
  - diazepam
  - fluconazole
  - fluoxetine
  - erythromycin
  - metronidazole
  - propoxyphene
  - Spironolactone
  - (grapefruit juice)  (Levitt, 2006)
How to Manage Acute Pain in Patients Receiving MMT?

Basic Principles

1) After verification continue daily MMT dosing without interruption

2) Appropriate and aggressive pain management

(Afford, et al, 2006)

Assess

- Pain (type, intensity, temporal characteristics)
- Pain management history
- Fears and anxieties
- Support systems
- Relapse risk factors
- Co-morbid physical pathologies
- Co-morbid psychopathologies
- Rx, OTC, and herbal preparations used
Allay Patient Fears
- Assure of continuing MMT methadone
- Assure that privacy will be respected
- Assure that appropriate pain management will be provided

Multimodal Analgesia
**CRITICAL ELEMENT**

**Acute Pain is a SYMPTOM**

Target the cause

Consider the specific type of pain being treated.

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**Non-Opioid Analgesia**

- Acetaminophen
- NSAIDS
- Adjuvant agents

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**Epidural or Regional Analgesia**

- Intra-operative
- Post-operative
  - Continuous infusion
  - PCEA or PCRA
- Infusion
  - Opioid
  - Local anesthetic
  - Combination
Topical Agents

- Local anesthetic
- NSAIDS
- Compounded agents

Opioid Analgesia

- Cornerstone of management of moderate to severe pain

- **Avoid** agonist and antagonist opioids

- Caution for opioids in combination

Considerations for Opioid Analgesia in Patients Receiving MMT

- Consider the pharmacokinetics of opioids
  - Cross tolerance of morphine
  - Avoid mixed agonists/antagonists
  - Probably avoid combination opioids

- Patients receiving MMT methadone therapy may require:
  - higher than usual doses of opioids
  - shorter than usual dose intervals

Delivery of Opioids

- Continuous or sustained release
- Scheduled vs prn
- Pre-emptive analgesia
- PCA
  - mixed empirical data
  - increases control
  - reduces anxiety


Non-pharm Interventions

- Prayer
- Mindfulness meditation
- Physical Exercise
- Stretching - yoga
- Herbs
- Acupuncture
- Counseling

(Barry et al, 2009)

Environmental Modifications

- hospital room = world
- position in their world
- temperature
- lighting
- quiet vs. sound/noise
- visitors vs. solitude
- activity vs. isolation
Caring Presence

Centered place
Compassion

**Intention to help**

Focused attention
Incite
Compassionate Insight!

Discharge from Acute Care
- Weaning plan
- Communication with MMT staff

Special Populations
- Pregnant women
- Co-morbid chronic pain
- Co-morbid physical diagnoses
- Co-morbid psychiatric diagnosis
- Elderly
I.R.

- 51 y/o
- restrained driver in single car MVA

PMH:
- emphysema r/t tobacco abuse
- IVDA (heroin)

Please,
Write down your description of IR.

I.R.

- 51 y/o **Caucasian female**
- **actual body weight 50 kg**
- restrained driver in single car MVA

PMH:
- **breast CA with mets to bone BLE & thorax**
- emphysema r/t tobacco abuse
- IVDA (heroin)
I.R. Pre admit meds

- Methadone 90 mg qd x 20 years
- Morphine ER 30 mg tid x 6 years
- Oxycodone w APAP 2 q 4 hrs prn pain (average 12 per day)

I. R. Analgesia Post admission

Morphine PCA:

4mg PCA dose
8 min LO
0 4 hour max

Pain Consult

- pain 11/10
- Assessed
- Started:
  - Hydromorphone PCA
    - Loading Dose of 2 mg then PCA doses of 0.1/8/0
  - Ketorolac
    - 30 mg stat
    - 15 mg q 6 hrs x 24
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<th>Pain</th>
<th>Dose</th>
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<th>Adjuvant</th>
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<td>Ketorolac</td>
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<td>Methadone 90 mg/ qd</td>
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<td>1.2</td>
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<td>Methadone 90 mg/ qd</td>
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<td>0.8</td>
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<td>2/10</td>
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<tr>
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<td>d/c</td>
<td>0</td>
<td>ER morphine 15mg tid</td>
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### Comparison of I.R. Opioids

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<th>Hospital D/C doses</th>
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<td>2 q hrs (12/day)</td>
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References


- SAMHSA. (2010). Similarities and differences in opioid treatment programs that provide methadone maintenance or buprenorphine maintenance.
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- http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5605a1.htm
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- http://www.eperc.mew.edu/fastFact/ff_75.htm
- http://pain-topics.org/opioid_rx/methadone.php#methintr