Methadone Use in 2011

Complexities, Controversies & Competencies

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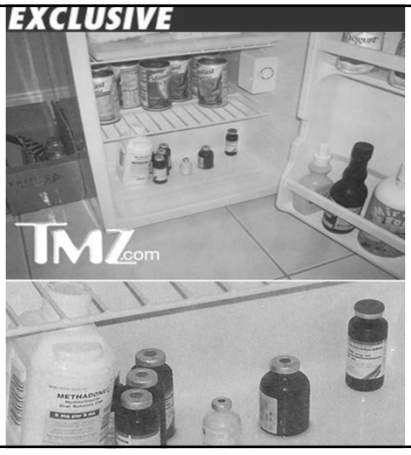
For Years I've Given a Talk Called: *Methadone Madness!!!*

Methadone Madness Objectives

- Case-based…great cases
- The drug
- Benefits
  - Why aren't we using this great drug?!
- Risks
- Particularly dosing concerns
- Parenteral methadone

Then…the "Madness" Got Crazier



"Celebrity" analgesic?

Even BANS… (Before Anna-Nicole & Son)

- Marked increase in "accidental" overdoses in many states
- NC among them – 5 fold rise 1997-2001 (*JAMA* 2003)
  - 12 in 1997; 80 in 2001
  - 75% prescribed by MD; 25% illicit
    - Just the opposite in other states, 25/75
- NC Death Certificates 2005 (NC Div of Public Health)
  - 872 fatal "poisonings" due to Narcotics
  - 31% cocaine and 30% methadone = 261
- Increase in prescriptions for analgesia not addiction
  - Utah traced most of the prescriptions in accidental methadone deaths to the offices of general practitioners

Notoriety…Aired on 20/20

Don't want it but better deal with it

The Dangers of Methadone

Parents try to help others by sharing story on TV of Parkland senior's death

By Tim Cloofelter
JOURNAL REPORTER

In October 2002, Terry and Lisa Houston went through every parent's worst nightmare — the death of a child.

Their son, Michael, died after taking methadone, a prescription drug used as a painkiller and to treat narcotic addiction.

On Friday, the Houstons will be on the television newsmagazine *20/20* to [illegible] They say they hope that they can [illegible] awareness of a little-known danger posed by the drug, which can lower respiration [illegible] ous degree in some people if too much medicine is taken or if it is taken incorrectly.

"It doesn't make sense that he's not still here," Terry Houston said. "And he would be if it weren't for those two little pills."

Earlier this year, the Houstons met with family members of other people in North Carolina who died after taking methadone, including a couple from Statesville and several people from the Eastern part of the state. Some, such as Michael, took drugs that had not been prescribed. Others had taken prescription doses but had unexpected complications [illegible] unless you've lost a child," Terry Houston said. "We exchanged phone numbers and business cards. Everybody was going through the same loss."

That loss has become more common in recent years as prescriptions of methadone have increased. According to N.C. State Center for Health Statistics, the number of overdose deaths in which methadone was a cause or a contributing factor has increased steadily in recent years.

In 2000, there were 74 such deaths statewide. That number increased to 272 in 2005.

Michael Houston was a 17-year-old senior at Parkland High School when he died after taking two methadone pills that were given to him by a friend, his father said. Michael had bronchitis [illegible] sleeping. He took the pills [illegible] hoped would help him get some sleep. His father said [illegible] his parents went to wake [illegible] that he was barely breathing. "We called 911," his father recalled. "He never regained consciousness."

See MICHAEL HOUSTON, Page E2

"KILLER DRUG" ***NYTimes*** **2002**

"WIDELY ABUSED AND DANGEROUS" ***Washington Times*** **2003**

17 y/o took two methadone pills from a friend because he'd been having Trouble sleeping secondary to "bronchitis"

W-S Journal 4/15/11 - Sports Section

MISCELLANEOUS

Family says Williams player died from medication overdose

Family members say a Burlington Williams quarterback died after a victory last month after accidentally overdosing on some of his grandmother's pain medication.

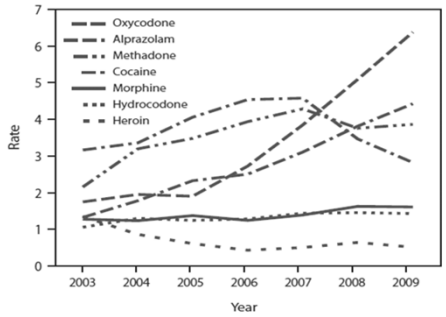
The family of **Harry Cohen** said the boy apparently took methadone the day after leading the football team to a 27-17 victory over Southern Alamance.

Richard Kaffenberger, Cohen's stepfather, said Cohen's 150-pound frame and low body fat meant the pain-fighting methadone he ingested had nowhere to go but his organs.

The Times-News of Burlington reported that Cohen's death certificate lists his cause of death as cardiopulmonary arrest because his heart stopped beating. The secondary cause is listed as methadone poisoning resulting from an accident.

Annual drug overdose death rates*

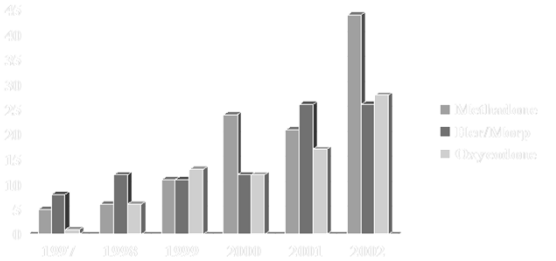
for selected prescription and illicit drugs --- Florida, 2003--2009



*per 100,000 population

ME "Singled out" along with NC and FL

Methadone-associated mortality: Report of National Assessment
Substance Abuse & Mental Health Services Admin (SAMHSA)



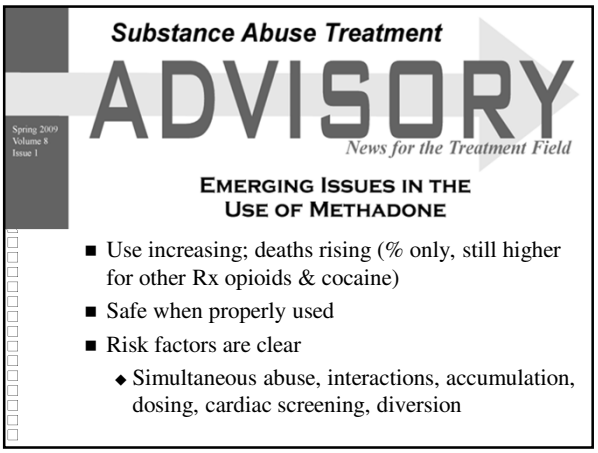
www.samhsa.gov

SAMHSA "Scenarios for Methadone Deaths"

- "Illicitly obtained methadone to achieve euphoria"
  - Illicit dosing errors to get high or prevent withdrawal
- "Illicit or licit use in combination with other prescription medications, alcohol, opioids, or benzodiazepines"
  - Illicit or licit ignorance of potential drug interactions
- "Accumulation of methadone to harmful serum levels in the first few days of treatment for addiction or pain"
  - Illicit or licit dosing errors in the opioid naive
- Reading between the lines
  - Failure of the Illicit or licit prescribers/users to recognize the unique properties of this opioid

All of this and More!
Led to: FDA Alert 11/06

- Methadone is effective; may provide pain relief when others have failed
- Significant toxicities
- Elimination half-life (8-59hrs) longer than analgesic action (4-8hrs).
- Cross-tolerance incomplete making conversion complex
- Complex drug interactions with many other medications
- May cause prolongation of QTc and even Torsades de Pointes



- Use increasing; deaths rising (% only, still higher for other Rx opioids & cocaine)
- Safe when properly used
- Risk factors are clear
  - Simultaneous abuse, interactions, accumulation, dosing, cardiac screening, diversion

In light of these events…
What's a conscientious pain provider to do?

- Respect the substance of the FDA alert
- It is what we teach!!! And the essence of competencies!
  - (How about a few Board questions????)
- "Methadone may provide relief where others have failed." = It may be better!
- Demands that we become competent, careful prescribers

To Use or Not to Use?
Therapeutic Index

- Advantages
  - Mechanism of action
    - ↓ Tolerance
    - ↓ Hyperalgesia
    - Neuropathic pain
  - ↓ risk toxicity
    - Neurotoxicity
    - Safe in ↓ renal
  - Rapid onset, but long-acting (q 8 hr – q 12 hr dosing)
  - Cost
  - Side effect profile
- Disadvantages
  - Interpatient variability (complex & prolonged conversion regimen)
  - ? Cardiotoxicity
  - Drug-drug interactions
  - Conversion ratio not fixed
  - Social stigma
  - Diversion

Case 1: (One of my first)
Complex Pain Made Simple (11/00)

- 46 y/o AA male with TR Cell CA Bladder
  - local invasion; liver; bone; lung
- S/P maximal medical therapy
- Most recent adm. pain crisis/bone metastases
  - RT to some of the areas
- Transferred to KBR for pain control and terminal care

Pain Assessment on Admission

- Location
  - 12 separate musculoskeletal locations
  - also "hurt all over"
- Intensity
  - W 10/10; L 6/10; A 8/10; N 8/10; Rx <50%
- Quality
  - Ache, burn, stab, gnawing
- Interferes with sleep, mood, visits, function
- Pain Hx (none); EtOH, Cocaine, AA

Medications

- MS by PCA 40mg/hr + 40mg bolus q15”
- MSContin 80mg bid PO
- Duragesic 100mcg/hr Transderm
- Actiq 200mcg prn OT (not taking)
- Bolusing record =
  - maxing out
  - i.e. 16/25 X 4hrs
- 200mg/hr = 4800mg/day = **14.4 gms PO/day!**

Examination

- Pleasant, well nourished
- Grimacing, twitching, jerking
- Hyper-alert, slightly agitated
- Abbreviated Mental Test Score
  - AMTS = 10/10 (correlates with MMSE)
- Pain with movement
- R frontal periosteal swelling; liver edge
- Nx; no DTRs but nonfocal

HELP!

- What’s going on!
- Opioids
  - consolidation
  - and/or rotation and hydration
- Opioid toxicity?
- Opioid sparing
  - Adjuvant analgesics
  - Non-pharmacologic measures

Case Continues…

- **IV Decadron and PO Neurontin**
- **Rotate to Dilaudid…and hydration**
- **Sx of opioid toxicity improved only transiently**
- **Gradual conversion to PO Methadone 40mg tid**
  - by 1/3 q24hours
- **Dramatic improvement in < 24 hours**
  - By day 2, pain to 0/10; no agitation, twitches or jerks
- **Meaningful family time**
  - Xmas shopping at the mall
  - Xmas eve at sister’s
  - sociospiritual opportunities
- **Died ~ 1 mos later (not well)**

Gotta learn about this drug!

Among Opioid Families Methadone is Unique

- Phenanthrene Derivatives
  - Morphine
  - Codeine
  - Hydrocodone
  - Hydromorphone
  - Oxycodone
- Phenylpiperidine Derivatives
  - Meperidine
  - Fentanyl
- Diphenylheptane Derivatives
  - Methadone

Unique…
Mechanism of Action

- *mu* opioid agonist…like most opioids
  - But also a *delta and kappa* opioid agonist
- **And an NMDA** receptor antagonist
- **And a** Serotonin & norepinephrine reuptake inhibitor
  - Descending tracts in periaquaductal gray (PAG)…TCAs

NMDA Receptors

- At resting membrane potentials, NMDA receptor is blocked by Mg ions
  - Activation requires glutamate & glycine binding
- Mg removed by depolarization & phosphorylation
  - Increased neuronal excitability
  - Glutamate stimulation, even at resting membrane potential
- Implicated in the development of tolerance to opioids
- Wind-up theory in persistent or chronic pain
- Particularly neuropathic pain

Neuropathic Pain

Clinical Implications of Methadone as NMDA-Receptor Antagonist

- May counteract opioid tolerance
  - reduced dose escalation compared to other opioids
  - reverses tolerance induced by other opioids
- May counteract hyperalgesia
- May be more effective than other opioids against neuropathic pain

More Benefits

- high bioavailability (79+/-11.7%)
- long half-life (30.4+/-16.3 h)
- no active metabolites
- fecal excretion
- highly lipophilic (only PO and IM approved)
- very inexpensive

Unique…Lack of Opioid Toxicity

Neely K, Roxe D: Palliative Care/Hospice and the Withdrawal of Dialysis. J Pall Med 2000:3:57-67.

Opioid	Metabolite	Comment
Meperidine	**Normeperidine**	Toxicity well established
Morphine	**M6G; M3G**	Toxicity in renal failure & dehydration
Hydromorphone	**HM3G**	Case reports of neuroexcitation ESRD ++
Fentanyl	**Norfentanyl**	Actions conjectured
Oxycodone	**Noroxycodone**	Neuroexcitatory
Methadone	**None Known**	**Fecal excretion**

Neuroexcitatory opioid metabolites may cause…

- Twitching
- Jerking
- Myoclonus
- Agitation
- Seizures
- Allodynia
- Antagonistic behavior (at the mu receptor)

The Cost of Drugs = 360mg MEDD
Unique Cost…and the winner is?

Medication	*Dose*	*Cost*
Oxycontin	6 X 40mg	$39.69
MSIR tabs	60 mg q4h	$ 7.56
Morphine 20 mg/ml	60 mg q4h	$10.71
Hydromorphone	16 mg q4h	$12.40
Oramorph SR	180 mg q12h	$16.64
MS Contin	200 mg q12h	$21.88
Oxycodone 20mg/ml	60 mg q4h	$24.02
Duragesic	175 ugq72h	$32.51
Methadone	10 mg q8h	$ 0.30

1 mg Methadone = 1 cent!

Why aren't we using this??!!
The Madness Continues…(Risks)

- Tremendous interpatient pharmacokinetic variability
- Poorly defined equianalgesic potency
- Potentially scary dosing/safety issues
- Drug interactions (coumadin-like)
  - Antifungals; antivirals increase effects
- QT_c interval concerns
- Not a patent drug
- No one is marketing it!

Dosing Dilemmas

- Half-life (30.4 +/- 16.3 h)
- Recommended dosing intervals (3-24h)
- Duration of analgesia for a single dose (4-6h)
- Brevity of analgesia relative to half-life
- Rapid absorption-distribution
- Accumulates in tissues (binds tightly)
  - peripheral reservoir sustains plasma conc.
  - initial q4h dosing may stretch to bid
  - importance of PRN dosing schemes!

Equianalgesic Conversions

- Older tables typically report
  - Parenteral - MS:Methadone::1:1
  - Oral - MS:Methadone::3:1 or 3:2
- Based on single-dose studies
- **Not applicable to chronic dosing!!!!**
- Methadone dosing changes dramatically the higher the dose of the prior opioid
  - Mu, Delta, Kappa, NMDA antagonist, reverses tolerance

Methadone mantra…

Behaves as a
Much!
Much!!
Much!!!
more powerful opioid
the *higher* the dose
of the *prior* opioid!

Suggested Dosing Guide for Opioid Tolerant Patients **Fast Fact #75 www.eperc.mcw.edu Gazelle & Fine**

Daily Oral MS equivalents	Conversion ration MS to Methadone
<100 mg	3:1
101-300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
>1000 mg	20:1

Due to incomplete cross-tolerance reduce initial dose 50% of calculated

…Dosing Methadone Safely; Drug Interactions

- Hepatic metabolism, type I cytochrome P450 group of enzymes
- Induces enzyme activity
- May increase serum levels of certain drugs
  - Desipramine
- Medications that increase methadone levels
  - Certain anitfungals, SSRIs, and others…
- Medications that decrease methadone levels
  - Alcohol (chronic), smoking, some anticonvulsants
- Synergistic toxicity – benzodiazepines
- Synergistic analgesia – dronabinol & ibuprofen

Inducers That May **Increase** Methadone Effects

- Cimetidine
- Ciprofloxacin
- Diazepam
- Diltiazem
- Disulfiram
- Ethanol (acute use)
- Fluconazole
- Grapefruit
- Haloperidol
- Ketoconazole
- Macrolides (Emycin)
- Metronidazole
- Omeprazole
- SSRIs
- Urinary alkalinizers
- Verapamil

Case reports of sedation, somnolence, respiratory depression, and death!

So don't take your:

Diflucan, Prilosec and Verapamil with a Salty Dog!

1 Part ABSOLUT VODKA
2 Parts Grapefruit Juice
1 Peel Grapefruit

Inducers That May **Decrease** Methadone Effects

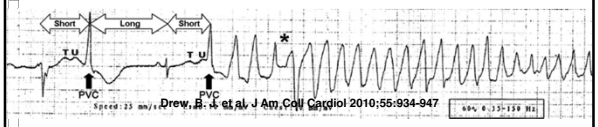
- Abacavir
- Amepravir
- Barbiturates
- Carbamazepine
- Cocaine
- Dexamethasone
- Efavirenz
- Ethanol (chronic use)
- Fusidica acid
- Heroin
- Lopinavir plus ritonavir
- Nelfinavir
- Nevirapine
- Phenytoin
- Rifampin
- Spironolactone
- St John's Wort
- Tobacco
- Urinary acidifiers

Case reports of increase pain, withdrawal symptoms, seizures

Prolonged QTc Interval

- A condition associated with development of ventricular tachycardia (TdP)
- Dose-related?
- Underlying heart disease?
- Other drugs (inhibitors of CyP450)
- Hypokalemia, liver disease
- Do our patients die of sudden death?
- How do our patients die?
- Start doing EKGs? Holters?

Onset of TdP during the recording of a standard 12-lead ECG in a young male with a history of drug addiction treated with chronic methadone therapy who presented to a hospital emergency department after ingesting an overdose of prescription and over-the-counter drugs from his parent's drug cabinet



Drew, B. J. et al. J Am Coll Cardiol 2010;55:934-947

Drugs we might prescribe with Risk of causing TdP

Generic Name	Brand Name	Clinical Use
Chlorpromazine	Thorazine	Antipsychotic
Clarithromycin	Biaxin	Antibiotic
Disopyramide	Norpace	Antiarrhythmic
Erythromycin	EES, Erythrocin	Antibiotic
Haloperidol	Haldol	Agitation, antiemetic
Methadone	Dolophine, Methadose	Analgesic, dependence
Sotalol	Betapace	Antiarrhythmic

More complete list at www.qtdrugs.org

Factors associated with a tendency to TdP

Familial long QT syndrome
Class IA antiarrhythmics
Class III antiarrhythmics
Hypomagnesemia
Hypokalemia
Hypocalcemia
Hypoxia
Acidosis
Heart failure
Left ventricular hypertrophy
Slow heart rate
Female gender
Hypothermia
Subarachnoid hemorrhage

Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc Time

Fredheim 2006 JPSM

- A prospective 9-month follow-up study
- Previously only case reports and retrospectives
- 8 chronic nonmalignant pain patients
- Insufficient pain control or intolerable side effects
- ECGs at baseline and follow-up
- Minor increase QTc; fluctuations; clinically insignificant; no arrhythmias

A community-based evaluation of sudden death associated with therapeutic methadone

Chugh et al Am J Med 2008

- Sudden death in Portland OR over 4 years
- Compared death with no methadone vs therapeutic levels
- Overdose & recreational use excluded
- Autopsy series
- Methadone group 23% had cardiac abnormalities associated with sudden death
- No methadone group…60%

TdP Conclusions for Oral Methadone

- Pay attention to risk factors
- Drug interactions
- Part of informed consent
- Routine EKGs probably not necessary

Scared? **Let's look at a few more cases of** ***Methadone Madness!!!***

Case 2: 50 y/o woman on Duragesic patches 300 mcg (3X100)

- She C/O cost!@#$!!%$#!!!!!
- $ 900/mos (maybe only $450 generic)
- Duragesic 300 mcg ~ 600 mg PO MS
- 10:1 = 60 mg Methadone
- 50% (inc. X-tolerance) = 30 mg Methadone
- Rx: Methadone 10 mg tid + 5mg q1h prn
- Stop patch start Methadone; both slow in slow out
- 30-50 cents/day (and she's in love!)
- Low dose methadone, but an elective conversion so some might do an EKG and f/u EKG

Case 3: 37 y/o WF, metastatic colon CA

- Metastases to omentum & pelvis
- Worst pains 10/10 to legs, somatic & neuropathic
- MS intrathecal pump switched to HM 5mg/day
- MS Contin 60mg PO tid
- Dilaudid 4mg PO bt X 5/day
- Actiq 1600mcg ~ 3/day
- Neurontin

Tough conversion calculation

- MS Contin easy = 180mg/day MS equivs
- HM PO easy = 7.5:30::20:X = 80 mg MS equivs
- Actiq 1600 mcg X3 =
  - 2/3 absorbed OT 1/3 PO
  - 1200 OX3 = 3600mcg = 100mcg:10mg MS (parenteral)::3600:X = 360mg X3 = 1080 MS equiv PO
- Grand Total = 1340 mg PO MS equivs/day
- 20:1 = 67 mg; reduce 50% = 30mg/day
- Methadone 10mg PO tid + 10mg q1-2hr prn BT

Outcomes: Dosing & pain control

- Admitted to KBR for conversion
- Start 10mg tid 10mg for BT
- Titrated up rapidly to 30mg tid + 20mg for BT
- Pain much better after 24 hours
- Insisted on DC day 3 to go home for her Birthday party day 4
- Day 6; pain 0-2; BT < daily; alert, oriented, no confusion, Happy Birthday!

Outcomes: Cost

HPCC Pharmacy cost/day (our costs are <<< AWP!)	
MS Contin 180mg	$ 11.07
Dilaudid 20mg	$ 3.05
Actiq 1600mcg X3	$ 73.88 Total = **$ 88.00/day**
Methadone 90mg	**$ 00.90/day** **90 cents/day!!!!!!!!!**

3 months later (good months)

- Re-admitted to KBR
- Increasing pain since Xmas
  - despite IT HM to 9mg/day
  - Methadone to 60mg PO tid
  - CT shows 20% increase in tumor
  - Pain is diffuse intra-abd + neuropathic to RLE
  - Functional decline, weakness and dysphagia
- Methadone PCA
- Lidocaine drip (woke next AM, ate breakfast!)

Bruera concludes, "situations in which methadone may be advantageous"

- Opioid-induced neurotoxicity
- Patients receiving high opioid doses
- Extended dosing interval
- Opioid-induced *tolerance*
- Neuropathic pain
- First line therapy
  - with experience

Role of Parenteral Methadone

- Challenged by patients on high dose opioids
- Poor pain control
  - Or even refractory pain
  - 2%(Portenoy)X1000 adm = 20/year
- Symptoms of opioid toxicity
- Unable to take PO
- If methadone is so great PO, why not IV?

Parenteral Methadone by PCA

- Dramatic conversions
  - We have treated > 400 patients over last 10 years
- Minimal literature
- "Should" be done as an inpatient
- Approach cautiously
- Maybe subcutaneous irritant
  - If true (?)
    - Add wee dose steroid to solution (1-2mg dexamethasone/day)
    - Or hyaluronidase (150 units occ bolus)

Methadone mantra…

Behaves as a
Much!
Much!!
Much!!!
more powerful opioid
the *higher* the dose
of the *prior* opioid!

Parenteral methadone…
The rules are the same

- Highly lipophilic
- C_{max} and "peak effect" faster than MS
- Analgesic $T^{1/2}$ ~ 6 hrs
- Large volume of distribution
- Binds to tissues and plasma proteins
- Plasma levels decline in biexponential fashion
- Careful equianalgesic conversions and plan for accumulation

Parenteral methadone literature… Not much!

- Case reports
  - Fitzgibbon 1997, high dose MS, refractory pain (1 pt), conversion 10:1
  - Manfredi 1996, HM (4 pts), refractory pain, conversion 5:1
  - Santiago-Palma 2001, fentanyl (20 pts), chronic pain, opioid rotation, conversion 25mcg:0.1mg methadone
- It makes sense!
- Other opioid PCAs with refractory pain almost always exceed 1000mg PO MEDD

A Review of Parenteral Methadone at KBR Hospice Home

- 160 patients treated 2000-2003
- Random sample of 24 reviewed
- 9 were conversions from PO methadone
  - Simple 2:1 conversion
- 3 were treated with intermittent bolus methadone
- 12 were converted to methadone by PCA
- 8 had very high previous opioid dose

8 Patients With High Dose Previous Opioid

- All dehydrated; all poor pain control
- 7 symptoms of opioid toxicity
- PO MS equivalents/24 hrs ranged:
  - 1,224 to 14,400 mg
- Final Methadone PCA doses ranged:
  - 1.5mg/hr to 16mg/hr (+IT bupiv/clon)

Outcomes

- 1 patient DC'd home
  - Colon CA; S/P A-P resect; pelvic recurrence
  - Adm on HM 11mg/hr + HM IT pump
  - Pain 9, Symptoms of toxicity
  - Went home "happy" on Methadone PCA 1.5mg/hr
  - Readmitted twice more
- 7 died; all from progression of far-advanced disease
- All more comfortable with appreciative families

Case 4: 60 y/o WF with Ovarian CA, mets to liver, bone & abd

- MS Contin + MSIR = hospitalized "tolerant" to MS
- Switch to Dilaudid PCA > DC on OxyContin and OxyIR
- Readmit to the hospital > Dilaudid PCA
  - Poor pain control; twitch, jerk, MC back arching
  - Dose to 50 mg/hr + 50 mg bolus q15"
    - (250/hr HM= 1,666/hr MS= 120,000mg PO MS/day)!!!
  - Ativan drip at 8 mg/hr

Transfer to KBR

- HM toxicity
  - HM 3-glucuronide (myoclonic jerks)
- Ativan drip?
  - Titrated up to treat iatrogenic symptoms!
- Converted to Methadone 10 mg/hr; Ativan prn
  - Rare bolus; rare early Ativan
  - No more moaning, groaning, twitching, "arching"
- Peaceful death (Methadone reduced to 5mg/hr)

Case 5: J N in *The Shining*

- 47 y/o WM; NSCLC; SVC Syndrome
- Admitted to hospital with pain, dyspnea & bizarre agitation
- High dose previous oral opioid
- Seen as PC Consult; MS 25mg/hr; actively dying
- Methadone 1mg/hr + Decadron; up to 3mg/hr
- Transfer to KBR
- Weaned gradually, became alert and comfortable
- Switched to PO; quality time with family
- Died 31 days later from progression of pulmonary disease on methadone 10mg IV tid

Methadone by PCA

- Can be safely done
- Highly lipophilic (fast)
- High volume of distribution (disappears)
- Binds to all tissues (reservoir)
- Achieves equilibrium
- Careful conversions
  - MS 20:1; HM 6:1; fentanyl 250mcg:1
- Base + bolus q15" (often a larger bolus to start)

Manfredi P. Methadone Injection Consensus Group. *AAHPM Bulletin* 2004;5:10-11.

Opioid rotation during chronic opioid therapy with IV patient-controlled analgesia (PCA): Safe and effective starting doses when rotating from other opioids to methadone.

Initial Opioid	Basal[a]	Basal[a]	Demand[b]	Cl Act B[c]
Morphine	10 mg	1 mg	1 mg	5 mg
Hydromorphone	1.5 mg	0.3 mg	0.3 mg	5 mg
Fentanyl	0.25 mg	1.25 mg	1.25 mg	5 mg

Note: Decrease the initial dose of methadone by 25-50% for high doses (50mg/hr morphine) & increase for low doses (5mg/hr)

a. Continuous hourly infusion
b. Dose available every 15 minutes by pressing the PCA button
c. Dose administered by the nurse upon request if the pain persists despite the use of demand doses

Consensus Guideline on Parenteral Methadone.

Shaiova L et al. *Pall Supp Care* 2008;6:165-176.

- Reiterated risks, benefits, dosing, & cautions
- Points increased risk of QTc with IV
- Implicates preservative chlorbutanol
- Suggests screening for cardiac risk factors + co-risk factors (meds, K+, Mg++)
- And periodic EKGs
  - Pre-, 24 hr, at steady state, at dose changes, change in condition
  - Controversial???? Informed patients and decision-making

PCA Methadone: Cost Effective?

Typical PCA pricing from your home infusion company

Drug	Quantity	Cost	EquiAnRx	EquiAn$
Morphine	1000mg/ 100ml	$125		$125
Dilaudid	1000mg/ 100ml	$395	10:1.5 150mg	$59
Methadone	1000mg/ 100ml	$103	20:1 50mg	$5

We've decided to start using "bagettes" of methadone!
And 1mg/ml to make conversions to 0.5mg/hr!

Going the other way?

- Converting back to "other" opioids
  - Patient/family request
  - IV Methadone shortage
- Moryl 2002 *Pain.* 12/13 patients switched back had uncontrolled pain and/or dysphoria. 12 switched back to methadone
- Hasn't worked well for us either
- Methadone to MS 1:1, then titrate up
- *Do not simply reverse dramatic conversions!!!!!*
  - Methadone, like ketamine, may reverse tolerance

What if methadone doesn't work?

- Rotate to IV Fentanyl
- Adjuvants
  - Steroids
  - Anticonvulsants
  - Ketamine
  - Toradol
  - Lidocaine
- Procedures
- Sedation
- Re-assess
  - Psychosocial and spiritual

Summary

- Methadone remains an important analgesic alternative for many of our patients
- Significant benefits
- Significant risks
- Careful patient selection
  - Good history taking; meds, habits, CVD
- Careful dosing & monitoring
- Patient and family education
- Competence!

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