Advanced Pain Prevention and Treatment in Pediatric Palliative Care: From Neuropathic, Visceral, Psycho-social-spiritual, and Chronic Pain

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Learning Objectives

• Explore difficult pain situations where opioid administration might not be indicated
• Discuss importance of multimodal, interdisciplinary, rehabilitative pain management in PPC
• Practice Methadone Prescription in Pediatrics

What are we measuring...?

(1) Nociceptive Pain: arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation
  - Somatic (for example, muscles, joints)
  - Chronic somatic pain typically well localized & often results from degenerative processes (such as arthritis)
  - Visceral (internal organs)

(2) Neuropathic Pain: resulting from injury to, or dysfunction of, the somatosensory system.
  - Central pain: caused by a lesion or disease of the central somatosensory nervous system

(3) Psycho-social-spiritual-emotional Pain / Total Pain

(4) Chronic Pain
  - Pain beyond expected time of healing
Case Example: Chronic-on-acute pain

- Roman (11-years old) Nov 2014 - March 2015
- Single left-ventricle, status post 3 palliative surgeries
- Protein-loosing enteropathy (PLE)
- Significant constant “wandering pain everywhere” (pain score VAS 8-10/10), plus chronic headache plus recurrent severe abdominal pain
- Missed > 40 days of school
- Deconditioned

Chronic Pain in Children

- Pain lasting > 3-6 months: Time definition arbitrary
- Pain that extends beyond the expected period of healing
- hence lacks the acute warning function of physiological nociception

Primary Pain Disorders

- Chronic daily headache
- Centrally mediated abdominal pain syndrome (2016)
- Chronic musculoskeletal pain (“fibromyalgia”)
  - CRPS ?
- Majority of children experience pain at multiple sites
Chronic-on-acute Pain

- Approximately 5% of children and teenagers in general population have significant pain related dysfunction.  

- At least (?) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, or cancer are expected to display chronic pain in addition to their underlying somatic pain episodes.

In USA: > 3.7 million children

- USA - Age 0-17: 74.3 million children (2014):  
  http://www.childstats.gov/americaschildren/tablespop1.asp

At least (!) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, or cancer are expected to display chronic pain in addition to their underlying somatic pain episodes.

Communication with Patient / Family

- Pain is real!
- First “function” gets better, then “pain” (not other way around)
- Positive Expectation = Self-fulfilling prophecy

Physical Therapy
- Daily home exercise

Integrative Medicine
- Self-hypnosis
- Biofeedback
- Progressive Muscle relaxation
- Daily home exercise
- Passive Massage, Acupuncture

Psychology (...if missing school)

Normalize Life
- Sports/Exercise
- Sleep-hygiene
- Social: Having daily fun
- School: Attending full-time (or school-re-entry plan)

Family Coaching

Medications...???
Medications ???

1. Low-dose Amitriptyline (stimulates)
2. Gabapentin (inhibits)
3. Acetaminophen
4. Ibuprofen (Celecoxib?)
5. Lidocain 5% patch
6. Melatonin
7. Vitamin D
8. Co-Q10, Fish-Oil/Omega 3000, Peppermint oil (coated) (for abdo pain?)

Exit Interview

Opioids in the absence of tissue injury or inflammation not indicated!

Roman - 3 1/2 months later
Neuropathic Pain

Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (IASP 2008)

- Grading System: (1) Definite, (2) Probable; (3) Possible
- (…but, not all lesions in the somatosensory system lead to neuropathic pain)

Prevalence

- Prevalence of neuropathic pain in children unclear
  - Probably not in infants...
    - Brachial plexus injury in newborns
    - Rats not before P7 to P21, i.e. 4-5 months in children...
    - Damage early on: no memory, adaptive immune system...?
Is it Neuropathic Pain...?


Potential Causes Include

- Spinal cord injury: “pain arising as a direct consequence of affecting the somatosensory system”

- Tumor related: direct tissue and nerve injury; advanced unresectable solid tumors


- Autoimmune and degenerative neuropathies: Guillain-Barré syndrome; Charcot-Marie-Tooth disease

- Metabolic neuropathies: toxic and metabolic neuropathies (eg, lead, mercury, alcohol, infection)

- Neurodegenerative disorders: Hereditary neurodegenerative disorders (Fabry disease, X-linked lysosomal disease caused by deficiency α-galactosidase), mitochondrial disorders, and primary erythromelalgia

- Cancer-directed chemotherapy, including

  - Vincristine: 50% painful peripheral neuropathy, muscle camps, numbness, tingling (hand, feet)

  - Cisplatin: Paresthesias in extremities
**Pharmacotherapy for neuropathic pain in adults**


<table>
<thead>
<tr>
<th>Medication (# of placebo controlled studies)</th>
<th># of participants</th>
<th>Pain Relief</th>
<th>Placebo</th>
<th>NNT</th>
<th>NNH</th>
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<td>Botulinum A (4)</td>
<td>137</td>
<td>60%</td>
<td>6%</td>
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<tr>
<td>TCAs (15)</td>
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<td>17.9%</td>
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<td>Strong Opioids (7)</td>
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<td>26.2%</td>
<td>4.3</td>
<td>11.7</td>
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<tr>
<td>Tramadol (6)</td>
<td>741</td>
<td>46.3%</td>
<td>26.6%</td>
<td>4.7</td>
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<tr>
<td>Gabapentin (14)</td>
<td>3503</td>
<td>34.7%</td>
<td>20.3%</td>
<td>6.3*</td>
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<td>Serotonin-noradrenaline reuptake inhibitor (10)</td>
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<td>Pregabalin (25)</td>
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<td>Capsaicin 8% (6)</td>
<td>2073</td>
<td>35.9%</td>
<td>27.4%</td>
<td>10.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

* extended release gabapentin NNT: 8; NNH: 31.8

ns=non significant

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**Management of Neuropathic Pain in Pediatrics**

Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
Integrative, rehabilitative & supportive therapies

- Expected part of treatment protocol; Age-appropriate modalities include
  - Physical (massage, TENS, comfort positioning, allowing family for close contact/touch)
  - Rehabilitation (physical therapy, occupational therapy)
  - Early increasing-intensity treadmill exercise reduces neuropathic pain (in rats) 
  - Behavioral (deep breathing, imagery, hypnosis, smartphone/tablet “apps”)
  - Acupressure, acupuncture, aromatherapy

In other words...

- Adult data: Despite best of care and sequential trials of pharmacological therapies: 40-60% of patients remain unrelieved or inadequately relieved (Dwokin et al. Pain 2007, 132:237-51)
- In the treatment of medium to severe neuropathic pain in children medications alone are not sufficient
- Management likely inefficient without:
  - PT/OT
  - Integrative Therapies
  - Psychological therapies (patient or parents)

Management of Neuropathic Pain in Pediatrics

Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Regional anesthesia, if appropriate
Regional anesthesia approaches to pain management in PC

- **Regional anesthesia:**
  - Central neuraxial infusions
  - Peripheral nerve and plexus blocks or infusions
  - Neurolytic blocks
  - Implanted intrathecal ports & pumps for baclofen, opioids, local anesthetics, and other adjuvants

- **Neurolytic Sympathectomy:**
  - RCT (n=109) inoperable abdominal or pelvic cancer: better pain control, less opioid consumption, and better quality of life

Management of Neuropathic Pain in Pediatrics

**Suggested “Non-Evidence-based” Step-by-Step Approach**

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Regional anesthesia, if appropriate
4. NEW! (a) suffix: Opioid analgesics (consider Tramadol or Methadone) plus NSAID

NSAIDs for Neuropathic Pain

Opioids for Neuropathic Pain

"Weak" opioids (multimechanism)
- Tramadol
  - NNT 4.7; NNH 6.3
- Tapentadol, Bias; NNT 10.2

"Strong" Opioids
- Morphine, oxycodone NNT 4.3; NNH 11.7
- No additional benefit > 180 mg morphine equivalents

Cochrane analysis: Oxycodone NOT effective as a pain medicine in diabetic neuropathy or postherpetic neuralgia

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Thalamus
NSAIDs
Acetaminophen (Paracetamol)

Periaqueductal grey (endorphins)
Opioids

Acetylsalicylic acid (ASA)

Integrative (non-pharmacological) therapies

Management of Neuropathic Pain in Pediatrics

Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Regional anaesthesia, if appropriate
4. NEW (1) onset: Opioid analgesics (consider Tramadol or Methadone) plus NSAID
5. (5) Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamines
Amitriptyline

- No dose-response effect
- Nortriptyline: only 1 study
- Efficacy of TCA in central pain


- n=39; superior efficacy of a nortriptyline-morphine combination over either monotherapy (plus gabapentinoid)


- 2 studies (high effect size): no effect of amitriptyline in HIV neuropathy


Amitriptyline (or Nortriptyline)

- Dosage: initial 0.1 mg/kg -> titrate to 0.4 mg/kg p.o. [max. 20-25 mg] (usually not up to 1-2 mg/kg/day) once at night -
- wean: decrease gradually!
- Effect: days - weeks; depends on length of symptoms
- Adverse effects: arrhythmia: EKG (QTC, WPW?), anticholinergic / antihistamine (dry mouth, constipation, blurred vision, sedation)
- Desipramine: anecdotal evidence of sudden death in children


Amitriptyline (or Nortriptyline)

Adverse effects: arrhythmia: EKG (QTC, WPW?), anticholinergic / antihistamine (dry mouth, constipation, blurred vision, sedation)

Management of Neuropathic Pain in Pediatrics  Suggested “Non-Evidence-based” Step-by-Step Approach

(1) Identify and treat underlying disease process (radiation?) (corticosteroids?)
(2) Integrative therapies & Rehabilitation: manage comorbidities (anxiety, sleep disturbances). Psychological Therapies.
(3) Regional anesthesia, if appropriate
(4) NEW (!) onset: Opioid analgesics (consider Tramadol or Methadone) plus NSAID
(5) Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
(6) Tricyclic Antidepressant and gabapentinoid

Gabapentinoids: Ca-channel α2-δ ligands

- Gabapentin: NNT: 6.3; NNH: 25.6
- Extended-release gabapentin: NNT 8.3; NNH 31.9
- No dose-response effect
- 15 studies (1468 participants) (post-herpetic neuralgia, diabetic neuropathy, cancer related neuropathic pain, phantom limb pain, Guillain Barré syndrome, spinal chord injury pain, various neuropathic pains)
- 42% improved compared to 19% on placebo
- NNT for effective pain relief in diabetic neuropathy 2.9; post herpetic neuralgia 1.9
### Pregabaline

- Efficacy worse than gabapentin
- NNT: 7.7, NNH: 13.9
- Negative RCTs: HIV neuropathy; central post-stroke pain
- Dose-response (600 mg/day more effective than 300 mg/day)
- Linear (pregabalin) versus non-linear (gabapentin) bioavailability: Clinical relevance unclear.
- Adverse effects include: Weight increase, dizziness, somnolence, blurred vision, life-threatening angioedema (face, mouth, larynx) - careful concurrent administration with ACE inhibitors

### Pediatric data

- 3 term & 8 preterm infants with suspected visceral hyperalgesia caused by variety of neurologic and gastrointestinal morbidities: Improved feeding tolerance and decreased irritability (2 bradycardia)
- Gabapentin appears to be an effective treatment for children with severe impairment of the CNS and recurrent pain behaviors, including intermittent changes in muscle tone

### Gabapentin

- Pediatric Dosage: gradually increasing from 3-5 mg/kg/dose TID to 10-20 mg/kg/dose TID, max. 1,200 mg/dose TID
- Infants: 4.5 mg PO Q6h (titrated to max. 15 mg Q6h)
- Example: 10-year-old girl, 30 kg
  - Day 1: 100 mg once daily
  - Day 2: 100 mg BID
  - Day 3: 100 mg TID
  - Day 4: 100-100-200 mg
  - Day 9: 300 mg TID

- wean: decrease gradually x 1-2 weeks!
- Effect: days - weeks
- Adverse effects include: ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, peripheral edema
Management of Neuropathic Pain in Pediatrics  Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Regional anesthesia, if appropriate
4. NEW (!) onset: Opioid analgesics [consider Tramadol or Methadone] plus NSAID
5. Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
6. Tricyclic Antidepressant and gabapentinoid
7. Lidocain patch (if localized pain).

Topical Lidocaine

- Produces selective, but incomplete block of A-delta and C fibers
- Cochran analysis: Small, short-term trials indicate topical lidocaine may be effective in treating neuropathic pain; safety & tolerability were good in all cases Derry S, Wiffen PJ, Moore RA, Quan H. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev 2014(7):CD010958.
Topical Lidocaine 5% patch

- RCT (n=87) effective adjunct in post-operative (knee replacement) pain management. Nafissi A: Lidoderm’s effectiveness in reducing pain in post-operative unilateral knee replacements patients. 30th Annual Scientific Meeting of the American Pain Society May 2011 (Poster)
- Not with severe hepatic dysfunction
- Side effects include skin problems (such as irritation and redness)
- For localized pain only
- Patch can be cut to fit
- 12 hours on/12 hours off [possibly longer?]

IV Lidocaine - Pediatric Experience

- Nausea after 4 days?
  Neuropathic Pain: 1 mg/kg over 5 min, then 1 mg/hr - target: 2-3 mcg/kg/min. Neupane D, Psaltis J, Frank L. Continuous lidocaine infusion for the relief of refractory malignant pain in children. The Journal of Supportive Oncology. 2004 Jan-Feb;2(1):90-4.
- Side effects:
  - Allergic reaction (serious, but rare), dose related: numbness around mouth, dizziness, slurring of speech, hallucinations, muscle twitches, seizures
  - Nausea after 4 days?

Management of Neuropathic Pain in Pediatrics

Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation? corticosteroids?)
3. Regional anesthesia, if appropriate
4. New (i.e.) inject: Opioid analgesics (consider Tramadol or Methadone) plus NSAID
5. NMDA-receptor-channel blocker [or agonist? IV lidocaine? Botox A? benzodiazepines? SNRIs? Capsaicin?]
6. Tricyclic antidepressant and gabapentinoid
7. Lidocain patch (if localized pain).
8. Tricyclic antidepressant or gabapentinoid + low-dose ketamine
9. NEW onset:
   - Opioid analgesics (consider Tramadol or Methadone) plus NSAID

- Identify and treat underlying disease process (radiation?)
- NMDA-receptor-channel blocker (or agonist?) IV lidocaine? Botox A? benzodiazepines? SNRIs? Capsaicin?
Central Sensitization


Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture [S(+)-enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]
- Sedative-Hypnotic- Dissociative Dosing: 1-2 mg/kg/ dose IV
- Analgesic (subanesthetic) Dosing: IV: 1-5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
- PO: 0.2-0.5 mg/kg TID-QID and PRN (xc, si, intranasal, pr, spinally)
- Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose?
Low-dose Ketamine

- Action which may contribute to analgesic effect:
  - Cholinergic transmission
  - Noradrenergic / serotonergic re-uptake inhibition
  - $\mu$, $\delta$, $\kappa$ - opioid-like effect
  - Interactions with other Na-/Ca- channels

Meller S, Pain 1996. 68:435-6

- Noradrenergic / serotonergic re-uptake inhibition

$\mu$, $\delta$, $\kappa$-opioid-like effect

Interactions with other Na-/Ca- channels

Low-dose Ketamine - Adult Evidence


Low-dose Ketamine - Pediatric Evidence

- no RCT’s, few case reports

- n = 11, terminal cancer, age 3-17

- Starting dose: 0.1-0.2 mg/kg/hr (max 1 mg/kg/hr)

- Lorazepam 0.025 mg/kg BID

- n = 8/11; $\downarrow$ Pain; $\downarrow$ Opioid requirements (28-100%)

- No psychotropic side effects, no hallucinations

Ketamine

- Steady-state oral/parenteral ratio unclear
- Bio-availability 93% IM/IV, 20% PO
- Potency ketamine:norketamine 3:1 (anesthetic); 1:1 (analgesic)
- Plasma half-life: ketamine 1-3 hrs; norketamine 12 hrs
- Maximum blood concentration of norketamine: oral > IV

Other Adjuvant Analgesics / Co-analgesics

Benzodiazepines (incl. diazepam, lorazepam, midazolam)
- Mechanisms of action: gamma-aminobutyric acid (GABA) receptors
  - Potentiation of GABA-mediated transmission: sedative, anxiolytic, and anticonvulsant actions
- Flumazenil, a competitive antagonist, can rapidly reverse (some of) the effects of benzodiazepines.
Nociceptive Pathways & Primary Sites of Action of Analgesics

**SNRI**

- Duloxetine, venlafaxine

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α-Adrenergic Agonists

**Analgesic effect?**

- Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory G-proteins

- Presynaptic alpha-2-adrenergic receptors reduce neurotransmitter release by inhibiting calcium influx

- Systemic alpha-2-adrenoceptor stimulation may facilitate inhibitory synaptic responses in the superficial dorsal horn to produce analgesia mediated by activation of the pontospinal noradrenergic inhibitory system
**α-2-Adrenergic Agonists: Clonidine vs Dexmedetomidine**

- **Dexmedetomidine** has greater α2- versus α1- selectivity than clonidine

- **Postoperative neuropathic pain crisis**

- **Metaanalysis:** Perioperative systemic alpha-2 agonists (clonidine or dexmedetomidine) decrease postoperative opioid consumption, pain intensity, and nausea. Recovery times are not prolonged. Common adverse effects are bradycardia and arterial hypotension. Clonidine increased risk of intraoperative (NNH 9) & postoperative hypotension (NNH 20). Dexmedetomidine increased the risk of postoperative bradycardia (NNH 3)

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**Clonidine**

- **PO:** 1-3 mcg/kg Q6h
- **Transdermal patch**: 4-12 mcg/kg/day [patches: 0.1, 0.2 or 0.3 mg/day - occluding smallest patch by 50%?]
- **IV:** not FDA approved
  - 1 mcg/kg/hr titrated to effect up to 3 mcg/kg/hr (Athens, Greece 5/16/2014)
  - Adult NHS Wolverhampton Guidelines starting dose 1 mcg/kg/h (up to 4 mcg/kg/hr)

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**Dexmedetomidine**

- **Used in palliative care**

- **Children’s of MN:** Dose 0.2-2 mcg/kg/hr IV

- **Rotation to clonidine:**
  - 0.1-0.6 mcg/kg/hr DEX = 1 mcg/kg/dose Q (4-) 6h CLONIDINE
  - 0.7-1.4 mcg/kg/hr DEX = 2 mcg/kg/dose Q (4-) 6h CLONIDINE
  - 1.5-2.0 mcg/kg/hr DEX = 3 mcg/kg/dose Q (4-) 6h CLONIDINE
Dexmedetomidine

- n=107 patients, age 3 days-17 years, retrospective review
  - Dexmedetomidine, as part of multi-modal management, appears to be safe and efficacious; providing analgesia and sedation throughout all pediatric age groups following cardiac surgery.
  - Overall well tolerated and safe with higher doses than previously noted [0.8 µg/kg/hr to 2.17 µg/kg/hr]
  - Also well tolerated by neonates, infants, and patients with Trisomy 21

Dexmedetomidine in Neonates

- Pharmacokinetics, safety, and efficacy of dexmedetomidine in preterm and term neonates at three dose levels between 0.2 µg/kg/hr and 0.5 µg/kg/hr: overall effective for sedating this population and it was well tolerated, different overall PK profile compared to older patients. Chrysostomou, C, Schulman, SR, Castellanos, MH, et al. (2013). A Phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. Journal of Pediatrics. Pii:S0022-3476(13)01230-4.

- Efficacy of fentanyl vs dexmedetomidine in patients less than 36 weeks gestational age at birth who were less than 2 weeks old at the study start and mechanically ventilated. mean duration 12.4 days, 0.3 – 1.2 µg /kg/hour (mean 0.6). O’Mara, K, Gal, P, Wimmer, J, et al. (2012). Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. J Pediatr Pharmacol Ther, 17(3): 252-262.
AAP Handout for parents "Despite relaxed regulations, marijuana harms developing brain":
http://aapnews.aappublications.org/content/36/3/4.full.pdf+html

Updated AAP policy opposes marijuana use, citing potential harms, lack of research

Botulinum toxin A

- Peripheral neuropathic pain
- 6 RCTs: 50-200 units s.c. in the region of pain
- Low placebo effect
- NNT: 1.9 [95% CI 1.5-2.5 for 4 studies]; one large (unpublished) study negative

# Adult Evidence Based Recommendations Neuropathic Pain

## First Line
- Tricyclic antidepressants
- Gabapentin, pregabalin
- Serotonin/norepinephrine reuptake inhibitors

## Second Line
- Tramadol
- Capsaicin 8%
- Lidocaine patch

## Third Line
- Strong opioids
- Botulinum toxin A


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## Advantages & Disadvantages of Methadone?

- Long acting
- Very effective in chronic pain relief
- Effective in neuropathic pain
- NMDA receptor blocker (helps preventing tolerance)
- Rapid onset of action (!)
- Lower incidence of constipation
- No active metabolites
- Safe in renal failure
- Safe in stable liver disease
- Incomplete cross tolerance (!)
- Inexpensive
Methadone: Disadvantages?

- Long half-life (may lead to accumulation; quick titration difficult)
- Wide dosing variation
- Equianalgesic conversion more complex
- Stigma?

Mechanism of Action

- $\mu$ ($\delta$, $\kappa$) - opioid receptor agonist (L [R-]methadone)
- NMDA-receptor antagonist (D-[S] and L-methadone)
- Presynaptic blocker of serotonin and norepinephrine re-uptake in periaqueductal gray (D-methadone)

Pharmacokinetics

- Oral bioavailability: 36-100% (usually > 60-90%)
- Peak plasma concentration: 1-7.5 hours
- Half-Life adults: mean 8-59 hours [4-190 hours]
- Onset of analgesia: 30-60 minutes
- Long half-life does NOT match the duration of analgesia (initially 4-6 hours; after repeated dosing 8-12 hours)
- No correlation between plasma concentration and dose or analgesic effect
Renal and/or hepatic impairment does not alter clearance or dosing of methadone (possibility in severe disease?)

Reservoir 99%
Liver Storage
Adipose Stores
Protein binding 60-90%
Alpha-1-acid-glycoprotein = acute phase reactant (elevated in cancer)

Methadone Drug Interaction

Inducers and Inhibitors of CYP enzymes

- **Decreases level**
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Risperidone
  - Autoinduction (clearance higher once reached steady-state)

- **Increases level**
  - SSRI
  - “Azols”
  - Macrolid antibiotics
  - Grapefruit juice
  - Nifedepin
  - Tricyclic antidepressants

Methadone - Conversion


- **Example**: 200 mg IV morphine/day = 600 mg PO/day
  - Discontinue current opioid
  - Start PO Methadone 10% of prior daily PO morphine dose PRN (max. 30 mg)
    - 30 mg PO STAT; then 30 mg Q3h PO PRN
  - On Day 6, calculate total amount of methadone taken during previous 48 hours and divide by 4 -> Dose Q12h
    - Day 4 & 5: 8 doses = 240 mg
      - 120 mg/d
      - 60 mg Q12h
  - With rescue dose “equal or smaller” Q3h PRN
    - 12-60 mg PRN Q3h
**Methadone Conversion- “The 30 mg Table”**
... actually 60mg ... reduced by 50-75% for incomplete cross tolerance

- Starting Dose (Opioid Naïve): 0.05-0.1 mg/kg/dose [2.5 - 5 mg PO Q6-12]

### Conversion Ratio:

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<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Estimated Daily Oral Methadone Requirement</th>
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<td>&lt; 100 mg</td>
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<tr>
<td>101mg - 300mg</td>
<td>5:1</td>
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<td>301mg - 600mg</td>
<td>10:1</td>
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<tr>
<td>601mg - 800mg</td>
<td>12:1</td>
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<tr>
<td>801mg - 1000mg</td>
<td>15:1</td>
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<tr>
<td>&gt; 1000mg</td>
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### Methadone Dose Ratio

- n=10 patients >1200 mg PO equivalent: No correlation was identified between high MED doses and methadone at dose stabilization after opioid rotation. A fixed maximum methadone dose of 30 mg/day produced clinically meaningful improvements in pain scores without adverse drug effects. Caution should be exercised before considering rotation to methadone doses higher than 30 mg/day in a patient receiving >1200 mg oral MED/day.

### Pediatric Case Study

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Estimated Daily Oral Methadone Requirement</th>
<th>Less</th>
<th>Target</th>
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<td>&lt; 100 mg</td>
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<td>10:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
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<td>101mg - 300mg</td>
<td>5:1</td>
<td>10:1</td>
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</tr>
<tr>
<td>301mg - 600mg</td>
<td>10:1</td>
<td>16:1</td>
<td>10:1</td>
<td></td>
</tr>
</tbody>
</table>

- 17 children 2-18 years
- PO: Day 5: total daily dose divided by 3 => Q8h plus 10% of daily dose Q2H PRN
- IV: 80% of PO dose; breakthrough 1/3- 1 of hourly dose

---

*Source: ROXANE LABORATORIES, INC.*
* Columus, OH 43216
* [http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/006134s028lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/006134s028lbl.pdf)*

Pediatric Case Studies

- Opioid conversion to methadone commonly practiced; dosing was significantly lower compared to adult conversion ratios; more than 40% of children were undermedicated; majority received opioids for sedation while intubated and ventilated; therefore safe and efficacious pediatric methadone conversion rates remain unclear.
  
  - Methadone (39% for neuropathic pain) was effective in treating both neuropathic and nociceptive pain that was unresponsive to other opioids.
  - Starting dose 0.06-3.8 mg/kg/day (median 0.32) PO/NG (IV x3)
  - 41% side effects: incl. sedation (n=10), nausea (6), constipation (6); no pruritus, no respiratory depression

Conversion to Methadone From Another Opioid

  
  - Day 1: Replace 1/3 of opioid dose with oral methadone on bid or tid schedule
  - Day 2: Replace next 1/3 of opioid dose.
  - Day 3: Complete change to methadone.

IV Methadone PCA

**INITIAL OPIOID** | **BASAL / hour** | **NEW OPIOID** | **BASAL / hour** | **PCA bolus (lockout 15 min)** | **CLINICIAN ACTIVATED BOLUS**
---|---|---|---|---|---
Morphine | 10 mg | Methadone | 1 mg | 1 mg | 5 mg
Hydromorphone | 1.5 mg | Methadone | 0.3 mg | 0.3 mg | 5 mg
Fentanyl | 250 mcg | Methadone | 1.25 mg | 1.25 mg | 5 mg

- ↓ methadone by 25-50% for high previous opioid doses (e.g. morphine 50 mg/hr)
- ↑ by 25-50% for low doses (e.g. 5 mg/hr morphine)
Methadone

Breakthrough dose...?
- Recommendations vary
- 10% of daily dose (1 interval) American Pain Society Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain 2008: 24-27
- Rescue dose equal or smaller BID dose Q3h PRN Morley J and Makin M (1998) Pain Reviews. 5:51-8

Methadone

Adverse effects
- Sedation, nausea, constipation
- Higher doses: opioid-induced neurotoxicity (myoclonus, hallucinations, nightmares), respiratory depression
- Hypoglycemia increased from 3.7 to 6.9% of patient days (of those 3% <40mg/dL/2.2 mmol/L) (>80% also other opioids) Moos, J., et al. Methadone Use and the Risk of Hypoglycemia for Inpatients With Cancer Pain. J Pain Symptom Manage. 2016. 51(1): p. 79-87 e1.

Route of Administration
- Oral
- Sublingual
- Rectal
- Intravenous

Analgesic Tolerance

To ECG or Not to ECG... That is Still the Question....

**Methadone**

**Cardiac Toxicity of Methadone**

**PO Methadone**
- QTc prolongation / torsades de pointes: Evidence limited to case reports
- No relation in retrospective study

**IV Methadone**
- Direct correlation between dose and QTc prolongation
- USA: commercial solution “Dolophine”: 1 mL = 10 mg methadone plus 5 mg chlorbutanol
- Chlorbutanol or chlorbutanol plus methadone rather than methadone alone, may be cause of cardiac toxicity?

**Cardiac Toxicity of Methadone**

- Prospective study: n=100 palliative care patients, 28% QTc prolongation at baseline; 1/64 (>500msec) at week 2; study supports the safety of methadone use for pain control in patients with advanced cancer in the palliative care setting [median dose @ week 2: 2.3 mg (1-90)]
- 1246 patients, F/U 12 months
  - Price LC, Palmer K (2014) J Pain Symptom Manage DOI: 10.1016/j.jpainsymman.2014.03.018
  - rate of QTc prolongation was 49.4%
  - 2.4% had a cardiac event
  - 50.4% were at risk for an event
  - Odds ratio: age (1.06), dose > 100mg/day (6.18)
Cardiac Toxicity of Methadone

- Caution should prevail - low threshold for EKG. Cruciani RA: Methadone To EKG or Not to EKG... That is Still the Question. J Pain Symptom Manage 2008. 36(5): 545-52
- Caution with inhibitors of CYP 2D6 and 3A4
  - SSRI
  - “Azols” (Fluconazol etc.)
  - Macrolid antibiotics
  - Grapefruit juice
- Nifedepin
- Tricyclic antidepressants

No grapefruit juice...?


- Specific recommendations
- use of alternative opioids in patients at high risk of complications related to corrected electrocardiographic QTc interval prolongation
- careful dose initiation and titration of methadone
- diligent monitoring and follow-up
- Monitoring all newborns born to mothers receiving methadone for NAS

- need to educate and counsel patients on methadone safety
- use of electrocardiography to identify persons at greater risk for methadone-associated arrhythmia
Center for Substance Abuse Treatment

- ECG at baseline, 30 days, annual
- ECG if > 100mg/d or unexplained syncopes/seizures
- QTc 450-500 ms: Discuss risks/benefits
- QTc > 500 ms: consider discontinuation or dose decrease


Neuroexcitatory Side-effects

Myoclonus with high-dose parenteral use observed:
- Dose reduction
- Change of application route
- ? Adjuvant use of ketamine


Questions...

- Does need for analgesia (at end of life) outweigh risk of cardiac toxicity?
- If excellent analgesia on conversion day 1 or 2 - consider dose reduction?
- Rescue dose: methadone or other opioid?
- PO: IV => 50% or 80%?
- Short duration of analgesia early in therapy:
  - Q4h day 1, Q6h day 2, Q8h day 3, (Q12h day 4)?
- Or previous opioid for breakthrough pain?
Methadone - Rotation to a Different Opioid

- don’t!
- 12/13 patients unable to complete rotation due to pain and dysphoria.
- 35/39 successful conversion; Methadone : oral morphine = 1:13.5 (IV); 1:4.7 (PO)
- Conversion from Methadone to other Opioid: Over 3 days reducing methadone by 1/3 per day!
- Switch to levorphanol?

• Conversion from Methadone to other Opioid: Over 3 days reducing methadone by 1/3 per day!

Jake

12-year-old Boy with metastatic neuroblastoma with increasing nociceptive (VAS 7/10) and neuropathic (VAS 9/10) pain; no over sedation

Current Opioids
- Fentanyl Patches: 2 x 100 mcg/hr Q72h
- Oxycodone ER: 30 mg BID PO
- Oxycodone/Acetaminophen (5/325mg): 7 tablets/day
- Morphine: 10 mg x 12/ day PO

Methadone Rotation

Meta-analysis 25 studies; mainly from uncontrolled observational studies
- One three-day switch (3DS) versus rapid conversion (RC)
- Success rates: 3DS-93%, RC-71.7%, and AL-92.8%
- Time to stable analgesia: RC <4.3 days and AL <6 days
Methadone Conversion- “The 30 mg Table”

... actually 60mg ... reduced by 50% for incomplete cross tolerance

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<tr>
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</tr>
<tr>
<td>601mg - 800mg</td>
<td>12:1</td>
</tr>
<tr>
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<td>15:1</td>
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Jake: Total Opioid Use in IV Morphine Equivalent

- Fentanyl Patches: 2 x 100mcg/hr Q72h
  200mcg/hr x 24 = 4800 mcg/day x 40 =

- Oxycodone ER: 30 mg BID PO
  = 60 mg/day

- Oxycodone/APAP (5/325mg): 7 tablets/day
  7 x 5 = 35 mg + 60 mg = 95mg/day =
  95 mg PO Morphine / 3 =

- Morphine: 10 mg x 12 / day
  10 x 12 = 120 mg /3 =

Total: 264 mg

Methadone Conversion- “The 30 mg Table”

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Jake [PO Methadone]

- 39 - 78 mg
- 60 mg
- 30 mg
- 10 mg PO Q8h
- 10% of 78 mg = 7.8 mg
- 35 mg PO Q1h PRN Morphine
- 1-5 mg PO Q3h PRN Methadone?

Alternatively:
Day 1: 5 mg PO Q4h
Day 2: 7.5 mg PO Q6h
Day 3: 10 mg PO Q8h

He had excellent pain control for 4 weeks on Methadone 12 mg PO Q8h (6mg PRN once every 2 days) - he develops significant nausea and vomiting and refuses to swallow medication

12 mg PO Q8h
6 mg PO Q3h PRN
12 mg SL/PR Q8h ???
6 mg SL Q3h PRN ?

12 mg PO Q8h 80%
9.6 mg IV Q8h
36 mg PO / Day
28.8 mg IV / Day
1.2 mg IV / hour

PCA Dose 1.2 mg
Lockout (15-) 30 min Max 2 -(4) boluses/hr

Jake would like to thank you for your excellent opioid analgesia management.

SERIOUSLY Awesome!
Low-dose Methadone & low-dose Haloperidol?

- n=43 patients; rotated to methadone 2.5 mg/day to 15 mg/day plus scheduled haloperidol (median: 1.5 mg/day) = improved analgesia

- Sigma (σ) receptors, initially described as a subtype of opioid receptors, are now considered unique receptors

- Haloperidol antagonism of sigma-1 = antinoceception in mice

- Sigma-1 Receptor antagonists remove binding to NR1 subunits of NMDA receptors, which prevents ability to restrain opioid-induced hyperalgesia

Clinical Chronic Pain

- Clinicians have historically considered most chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation), and now data increasingly suggest this is simply not the case
- Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders
- Opioids in the absence of tissue injury or inflammation are contraindicated!
- Importance of rehabilitative, interdisciplinary team approach

Conclusions Neuropathic Pain

- Neuropathic pain often under-assessed and under-treated
- Treat underlying cause, if possible and appropriate
- Careful step-by-step approach (combining integrative, rehabilitative, pharmacological and interventional therapies) warranted
- First Line medications: Amitriptyline, Gabapentin, (Opioids ?)
- Apply WHO principles for acute pain
- Low-dose Ketamine may represent a potent adjuvant analgesia
- Possible Indications: Neuropathic & Nociceptive Pain
- May reverse Opioid-induced hyperalgesia & Opioid tolerance: ↑ opioid efficacy ⇒ ↓ opioid adverse effects
Conclusions - Methadone

- Excellent opioid choice in the hands of experienced practitioner
- With close monitoring, methadone therapy can be done safely in pediatric patient populations in both inpatient and outpatient settings
- Advantages
  - High effectiveness in chronic pain relief as well as in the management of neuropathic pain
  - NMDA receptor antagonist mechanism (helps preventing tolerance)
  - Lower incidence of constipation
- Disadvantages
  - Long half-life (may lead to accumulation; making quick titration difficult)
  - More complex equianalgesic conversion, which requires a much longer and closer patient observation than other opioids.

Methadone should not be prescribed by those unfamiliar with its use!

Its effects should be closely monitored for several days, particularly when it is first started and after any dose changes.

Opioid rotation: Maximum starting dose of methadone usually not above 30 mg PO / day

Further Training: CIPPC@ChildrensMN.org

10th Annual Pediatric Pain Master Class
- Minneapolis, Minnesota, USA | June 17-23, 2017

Education in Palliative & End-of-life Care (EPEC): Become an EPEC-Pediatrics Trainer
- Coimbatore, India, Feb 8-9, 2017
- Montréal, Québec, Canada | April 29-30, 2017 (Professional Development Workshop: 04/28/17)