From Myth to Multimodal Analgesia: Treating Pain in Children

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Learning Objectives

• Evaluate assumptions about opioid use in children ["Attitude"]

• Discuss how multiple agents, interventions, rehabilitation, psychological & integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than a single analgesic or modality - and improves patient experience ["Knowledge"]

• Practice morphine prescription in case example ["Skill"]
So, how do we treat the individual pain patient in front of us?

Hmhh... Spoiler Alert: Crystal-clear answer on 3rd last slide!

Pediatric Pain - Status Quo

- Under treatment of pain in children
- Parents expect pain to be relieved
- Priorities of parents of hospitalized children “Taking care of pain” rated as second highest priority (1st: getting right diagnosis)

Parents’ greatest distress: failing to protect their child from pain

Assumption: everything possible is done

Pediatric Pain - Status Quo

- USA: adults receive more than two - three times as many analgesic doses as children (with identical diagnoses)
- Compared to adults, pediatric patients receive fewer and/or incorrectly dosed analgesics in daily routine
- The younger children are, the less likely they receive appropriate analgesia

- Parents’ greatest distress: failing to protect their child from pain
- Assumption: everything possible is done
Inappropriate Analgesia: Why Bother...

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression. [1946 Medical Research Council and 1958 National Child Development Study]


Myths and Barriers to Using Opioids

Case Scenario:

- You are taking care of a child in a hospital with severe acute somatic nociceptive pain. It crosses your mind to administer a strong opioid such as morphine, fentanyl, or hydromorphone.

- What would be the most common concerns you might hear from your colleagues or parents arguing against opioid use in this child?

Common Opioid Assumptions

- **Addiction**: "Chronic relapsing condition characterized by persistent, compulsive dependence on a behavior or substance despite adverse consequences.

- **Tolerance ≠ addiction**

- **Pseudo-addiction**

- **Over Sedation / Respiratory Depression**

- **Ileus / Constipation**

- **Medication “Too strong”**

- **Masking symptoms**

- **Abdominal Pain**

- **Opioids after major cranial surgery in children do NOT result in altered mental status nor respiratory depression**

- **As always...Think first! (e.g. compartment syndrome?)... analgesia second..."
How Do We Manage Acute Pain in Children?

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

- Data suggests that applying the World Health Organization (WHO) principles of pain management result in good pain relief for a large majority of children with cancer.
- In addition there is emerging evidence, that these principles are equally effective in acute pediatric pain management for non-malignant conditions.


WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

- Dosing at regular intervals (“By the Clock”)
- Adapting treatment to the individual child (“With the Child”)
- Using the appropriate route of administration (“By the appropriate route”)
- Using a two-step strategy (“By the Analgesic Ladder”)
WHO Principle 1: Dosing at Regular Intervals

- PRN (pro re data = “as needed”)
- PRN = Patient Receives Nothing
- When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals
- “By the clock” and NOT as an “as needed” (or pro re nata “PRN”) basis
- Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing
- PRN (as needed) only:
  - May take several hours & higher opioid doses to relieve pain
  - Results in cycle of undermedication and pain, alternating with periods of overmedication and drug toxicity


WHO Principle 2: Adapting Treatment to the Individual Child

- Treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis
- At analgesic dosing: no sedation expected
- The effective dose is what relieves the pain
- Different children may respond differently to same dose
- Effective dose must be adjusted to child’s needs
- Dose of strong opioids: only the sky is the limit
- Assess response frequently
- Pain Scales
- Look for opioid-induced side effects and toxicity

Regular (!) Pain Assessment

- One-dimensional self-report scores
- Multi-dimensional rating scores
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

Pain in children with impaired communication

- Non-communicating Children's Pain Checklist - Revised (NCCPC-R); postoperative Version (NCCPC-PV)
- Pediatric Pain Profile (PPP)
- r-FLACC

WHO Principle 3: Route of Administration
WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

- Dosing at regular intervals (“By the Clock”)
- Adapting treatment to the individual child (“With the Child”)
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- Using a two-step strategy (“By the Analgesic Ladder”)

WHO Principle 4: Using a Two-Step Strategy

**WHO Step 1**
Mild Pain

**Ibuprofen**
and/or
**Acetaminophen** *(Paracetamol)*

Other NSAIDs? Cox-2 Inhibitor?

Nociceptive Pathways & Primary Sites of Action of Analgesics

Thalamus

Acetaminophen *(Paracetamol)*

Injury

NSAIDs
Citius, Altius, Fortius...?

- Ibuprofen salts: fast-acting formulations
  - e.g. Advil® Film-Coated Tablets: 266 mg ibuprofen sodium (=200 mg of standard ibuprofen)
  - Produced significantly better analgesia over 6h, fewer re-medications than standard formulations
  - 200-mg fast-acting ibuprofen (NNT 2.1; 95% confidence interval 1.9-2.4) was as effective as 400 mg standard ibuprofen (NNT 2.4; 95% CI 2.2-2.5), with faster onset of analgesia.
- More rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events.
- However, earlier onset preferred in other pain condition, such as chronic nociceptive or neuropathic pain.

WHO Principle 1: Using a Two-Step Strategy

**WHO Step 1**
Mild Pain

- Ibuprofen and/or Acetaminophen (Paracetamol)
- Other NSAIDs? Cox-2 Inhibitor?

**WHO Step 2**
Moderate to Severe Pain

- Morphine
  - or fentanyl, hydromorphone, oxycodone, methadone

Multimodal (Opioid-sparing) Analgesia

- Non-Opioids
  - Acetaminophen / Paracetamol
  - NSAIDs

- Opioids
  - Tramadol ("weak")
  - Morphine ("strong")

4 WHO-Principles
- "By the clock"

Integrative Therapies
- Such as:
  - Massage
  - Distraction
  - Deep Breathing
  - Biofeedback
  - Aromatherapy
  - Hypnosis
Integrative Pain Management

State of the art pain management in the 21st century demands that pharmacological management must be combined with supportive and integrative, non-pharmacological therapies to manage a child's pain.

- Physical methods (e.g. cuddle/hug, massage, comfort positioning, heat, cold, TENS)
- Cognitive behavioral techniques (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback)
- Acupuncture, acupressure, aromatherapy

Integrative Pain & Symptom Management


Nociceptive Pathways & Primary Sites of Action of Analgesics

Descending pathways that modulate transmission of nociceptive signals originate in periaqueductal gray, locus coeruleus, posterior hypothalamus, and anterior cingulate cortex. These pathways are relayed through brainstem nuclei in the PEG and medulla to spinal cord. Inhibitory transmitters involved in these pathways incl. norepinephrine, 5-hydroxytryptamine, dopamine, & endogenous opioids.

Integrative (non-pharmacological) therapies

- Periaqueductal grey (endorphins)
- Acetaminophen (Paracetamol)
How does this stuff work...?


• Distraction significantly increased activation of cingulo-frontal cortex including orbitofrontal & perigenual anterior cingulate cortex (ACC), as well as periaqueductal gray (PAG) & the posterior thalamus.


\[A\delta\text{ or } C\text{ fiber}\]

Nociceptive Pathways & Primary Sites of Action of Analgesics

CORTEX: Spinal
- Anxiety
- Catastrophizing
- Depression
- Perceived injustices
- Disturbed Sleep

Thalamus

"OFF"

Periaqueductal grey (endorphins)

Integrative (non-pharmacological) therapies

"ON"

Opioids

Acetaminophen (Paracetamol)

NSAIDs

NSAIDs

Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Opioids
- Tramadol ("weak")
- Morphine ("strong")

4 WHO-Principles
- "By the clock"

Regional Anesthesia
- Neuraxial infusion
- Peripheral/Plexus Nerve block
- Neurolytic block
- Intrathecal port/pump
- Intraventricular opioids?
- Percutaneous cervical cordotomy?

Integrative Therapies
Such as:
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Speech Therapy

Psychology
- CBT
Regional anesthesia approaches to pain management in PC


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

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Integrative Therapies
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Psychology - CBT
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Child Life

Rehabilitation

Opioids
- Tramadol (weak)
- Morphine (strong)

4 WHO Principles
- “By the clock”

Regional Anesthesia
- Neuromaxial infusion
- Peripheral/Plexus Nerve block
- Neurolytic block
- Intrathecal port/pump
- Intraventricular opioids
- Perineural/local anesthetics

Adjuvants
- Alpha-Agonist
- Gabapentinoids
- TCA/Antidepressants
- NMDA-Antagonists
- Na-channel blockers
- Antispasmodics
- Benzodiazepines
- Phenothiazines
- Radioisotopes
- Bisphosphonates

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Child Life

Psychology
- CBT

No Needless Pain.
That's why we're called Multimodal Analgesia

No Needless Pain
So, how do we treat the individual pain patient in front of us?

Crystal clear answer:

"It Depends"  
-Socrates

Small Group work, please

Case Example 1: Andrea

- 10-year-old girl in severe acute (!) pain (e.g., metastasized osteosarcoma, sickle cell crisis); weight: 20 kg
- PCA pump currently not available
- Choice of opioid?
  - Immediate release morphine
  - ...unless...
Case Example Morphine

- Route of administration?
- Per kg dosing: Maximum 50 kg (!)
- Lean weight for obese children
- Please write the order (small group work)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Initial Pediatric Dose</th>
<th>Initial Adult Dose</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>IV, SC, ( PO \text{ as } \text{ needed} )</td>
<td>( 0.05 - 0.1 \text{ mg/kg} )</td>
<td>( 0.15 - 0.2 \text{ mg/kg} )</td>
<td>2 - 4h</td>
</tr>
</tbody>
</table>

Case Example Morphine (Immediate Release)

**Scheduled (round-the-clock) dose**
- IV: \( 0.1 \text{ mg} \times 20 \text{ kg} = 2 \text{ mg Q4h} \) (= 12 mg/day)
- PO: \( 0.3 \text{ mg} \times 20 \text{ kg} = 6 \text{ mg Q4h} \) (= 36 mg/day)

**Breakthrough (rescue) dose** = 1/10 - 1/6 of daily dose (Q1-2h)
- IV: \( 1.2 - 2 \text{ mg} \) \( 1.2 \text{ mg Q1h PRN} \)
- PO: \( 3.6 - 6 \text{ mg} \) \( 3.6 \text{ mg Q1h PRN} \)

if pain score > ...?..../10 and no signs of over sedation

Case Example Morphine

- **0300 hrs:** Pain Score 10/10 -> 2 mg IV \( [\text{or 6 mg PO}] \)
- **0400 hrs:** Pain Score 8/10 -> 1.2 mg IV \( [\text{or 3.6 mg PO}] \)
- **0500 hrs:** Pain Score 7/10 -> 1.2 mg IV \( [\text{or 3.6 mg PO}] \)
- **0600 hrs:** Pain Score 6/10 -> 1.2 mg IV \( [\text{or 3.6 mg PO}] \)
- **0700 hrs:** Pain Score 5/10

- Do I need to increase the dose?
- Crystal clear answer: ...It depends...!
Opioid Dose Escalation for Acute (!) Pain

- How to increase the dose?
  - 50 per cent rule!
  - ...However, depends on clinical scenario...
  - 2 mg IV Q4h -> 3 mg IV Q4h
  - 1.2 mg IV Q1 (-2)h PRN -> 1.8 mg IV Q1 (-2)h PRN

“IT DEPENDS”
- Socrates

Case Example 2: Sean

- 10-year-old boy in severe acute (!) pain (e.g. metastasized osteosarcoma, sickle cell crisis); weight: 20 kg
- PCA pump now available
- Question: PCA bolus only or continuous infusion plus PCA bolus?

Meta-Analysis: Addition of continuous (or background) infusion to the demand (or PCA bolus) dose for IV-PCA is NOT associated with a higher incidence of respiratory events than PCA bolus alone in pediatric patients (in contrast to adults).


PCA with a CADD can be used to manage pain in the home setting. Dose adjustments and opioid switches were performed with no adverse incidents.

PCA-Pumps in Infants, Children and Teenagers

- WHO Principle 1: Dosing at Regular Intervals
- Rule of thumb: Management of acute medium-severe (!) pain in children with PCA pumps: USUALLY start continuous infusion PLUS on-demand PCA bolus.
- However, PCA only:
  - Part of multimodal postoperative analgesia (e.g. nerve block, scheduled acetaminophen / NSAIDs, dexmedetomidine etc...)
  - Incidence pain only
  - Weaning opioid / rotating to oral administration
  - Unclear pain pathophysiology...
  - Other...?
Please write PCA Order

- **Morphine** (and Plan B: Fentanyl and Plan C: Hydromorphone)
- Patient (or nurse-) controlled analgesia: PCA

1. Continuous Infusion
2. PCA- Dose
3. Lock-Out Time
4. Maximum number of boluses per hour

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Continuous Infusion / PCA Dose

1. Background (continuous) infusion i.v./s.c.:
   - **Morphine**: 15-20 mcg x 20 kg = 0.3-0.4 mg/hr
   - **Fentanyl**: 0.5-1 mcg x 20 kg = 10 - 20 mcg/hr
   - **Hydromorphone**: 2-5 mcg x 20 kg = 40 - 100 mcg
2. PCA- Dose
   - Same as above / hourly dose (e.g. 0.4 mg morphine)
   - Unless there is a good reason not to...

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PCA Order Set

1. Lockout time:
   - 5 - 10 minutes
2. Maximum number of boluses per hour:
   - 4 (-6) ...however, depends on the clinical scenario
   - **Loading dose**: ...depends... (hourly dose x 1-4...)
   - **Lower starting dose**: ...depends... age... if multimodal analgesia...
   - **How to increase the dose**?
     - 50 per cent rule
Finally…

- Andrea & Sean would like to thank you for your excellent pain management

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Example for 50% titration orders:

- Patient (or nurse-) controlled analgesia: PCA
- Background infusion i.v./s.c.: 0.4 mg/hr
- Bolus i.v./s.c.: 0.4 mg (max 6 per hour); Lockout time: 5 (-10) minutes

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Example for 50% titration orders:

- If receiving > __ boluses/hour for > __ consecutive hours AND if unrelieved pain AND no over sedation or dose limiting side effects, increase PCA by 50% as follows:

  - **Step 1:** Continuous infusion 0.6 mg/hr, PCA dose 0.6 mg, max. 6 boluses/hr
  - **Step 2:** (if ↑ again) Continuous infusion 0.9 mg/hr, PCA dose 0.9 mg, max. 6 boluses/hr
  - **Step 3:** (if ↑ again) Continuous infusion 1.35 mg/hr, PCA dose 1.35 mg, max. 6 boluses/hr

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Conclusions

- Withholding evidence-based analgesia from hospitalized children in pain suffering from serious hematologic/oncologic diseases not only unethical, but causes immediate and long-term harm
- Potential risks in safety of analgesics are real, but manageable; cannot justify denying administration of pain medications to pediatric patients
- Opioids (outside end-of-life) usually short term only - contraindicated for chronic pain
- Use multimodal (opioid-sparing) analgesia: Multiple agents, interventions, rehabilitation, psychological and integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality
With profound gratitude to our interdisciplinary Pain, Palliative & Integrative Medicine team

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**Admin Assistants**
- Katie McQuire
- Cheryl Puumala

**Clinic Staff**
- Brock Hebert
- Allison McQuade

**Manager**
- Tracey Crocoll
- Liz Leghtos, RN

Further Links

- Video: Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic Tour https://vimeo.com/122654881
- Short Movie Meet the Interdisciplinary Chronic Pain Clinic Team at Children’s Minnesota: LittleStars TV https://www.youtube.com/watch?v=136vBq1n9dw
- Video/Tour of the Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic at Children’s Hospitals and Clinics of Minnesota and an overview of the three programs that are offered at Children’s under this clinic: https://vimeo.com/11390794
- Short Movie LydiasDiaryFilm’s Kali’s Story - Beyond the NICU. This amazing pediatric palliative care short movie (7 min) features 8-year-old Kali’s journey at Children’s Hospitals and Clinics of Minnesota from NICU to today, receiving care by the Pain & Palliative & Integrative Medicine program while inpatient, in the clinic, and at home (Jun 22, 2015) http://www.lettsters.org/shorts/ludasbeyond-the-nicu

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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
- Montréal, Québec, Canada | April 29-30, 2017 (Professional Development Workshop: 04/28/17)