Pediatric Pain Management: Pearls, Pitfalls & Progress

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My Two Pertinent Disclosures

1. I do not have a financial relationship or interest with any proprietary entity producing healthcare goods or services in conjunction with this presentation.

2. I will be discussing the off-label, pediatric use of FDA-approved pharmaceuticals. Such use requires a thorough review of the published literature in adults, adolescents, and children.

My Present Learner Objectives

• To describe the continued challenges and barriers to providing effective pediatric pain management

• To identify clinically significant pediatric opioid analgesic metabolism

• To assess how to balance safety and quality in pediatric pain management

• To characterize recent current trends in the demographics and phenomenon of pediatric chronic pain
Psychological and Social Barriers to Optimal Pain Management in Infants and Children: Then & Now?

- **COGNITIVE DEVELOPMENT BARRIERS**
  - Inability of children to understand the nature of their pain and to quantify perception of pain

- **EMOTIONAL DEVELOPMENTAL BARRIERS**
  - Presence of both pain and a anxiety/depression increases the risk that either pain or the psychiatric disorder will not receive adequate treatment

- **PERCEIVED LACK OF CONTROL**
  - Perceived lack of control by children in health care situations is likely to promote feeling helpless and to enhance pain perception and anxiety about pain

- **CHILDREN NOT DISCLOSING PAIN**
  - Children and adolescents may not communicate their pain because of worries about the meaning of their pain – including that their pain is a punishment for misdeeds

- **CHILDREN’S KNOWLEDGE, ATTITUDES, AND BELIEFS**
  - Children and adolescents are given very little instruction in pain management prior to surgery and may believe that pain is inevitable and nothing can be done about it

Barriers to Effective Pediatric Pain Management Continue in 2010’s

- Variability in practice and continued outmoded beliefs
- Newborn infants do not experience pain
- Children rarely require analgesia
- Pain is merely a symptom and not necessarily harmful in itself
- Effective analgesia
  - Is dangerous
  - Makes diagnosis difficult or impossible
  - Delays discharge
- Postoperative analgesia
  - Not prescribed
  - Prescribed in doses too low or too infrequent
  - Not administered because pain not assessed

Developing a Pediatric Pain Service

- **Major obstacles:** Institutional acknowledgement and desire to change, appropriate staffing, and funding
- Important to determine whether the proposed service intends to treat acute, chronic, procedural, and/or cancer and palliative pain as each requires different skills and resources
- **It is not feasible or necessary for every hospital to manage all aspects of pediatric pain.**
- Remains a need for better pain management in facilities and geographic locations with fewer resources
Greater awareness is needed of the inadequate pediatric acute and chronic pain management in the developing world.
### Availability and Gaps of Pediatric Palliative Care in Low- and Middle-Income Countries

- Reported availability of pediatric palliative care services in 30 distinct programs in 21 low- and middle-income countries

<table>
<thead>
<tr>
<th>Domain</th>
<th>Availability</th>
<th>Gaps</th>
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<tbody>
<tr>
<td>Access</td>
<td>Present</td>
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<tr>
<td>Education</td>
<td>Present</td>
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<td>Health system support</td>
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<td>Pain management</td>
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<td>Symptom management</td>
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<td>End-of-life care</td>
<td>Present</td>
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<tr>
<td>Bereavement</td>
<td>Present</td>
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</table>

15 items across 7 domains

1. Access
2. Education
3. Health system support
4. Pain management
5. Symptom management
6. End-of-life care
7. Bereavement

### CYP2D6 Isoenzyme

- One of the cytochrome (CYP) P450 isoenzymes
- CYP2D6 responsible for Phase I O-demethylation
- Converts several pro-drugs into active metabolites:
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Tramadol

- Oxycodone, hydromorphone & oxymorphone do not require metabolism to be active analgesics.

Oxymorphone has 40X higher affinity for µ opioid receptor than oxycodone.

### Metabolic Pathways of Codeine, Morphine, and Hydrocodone

- Codeine
- Morphine
- Hydrocodone

- UGT: uridinediphosphate-glucuronosyltransferase

Metabolic Pathways of Oxycodone and Oxymorphone

AUC and Cmax for oxymorphone and noroxymorphone metabolites correlated with CYP2D6 + 3A4 activity

Noroxycodone has very low μ opioid receptor affinity

Noroxymorphone poorly penetrates the blood-brain barrier

CYP2D6 Genetic Polymorphism

• CYP2D6 critical for opioid effectiveness and toxicity
• Patients are classified into the following 4 categories of CYP2D6 activity, from highest to lowest functioning:
  ◦ Ultra-rapid metabolizer (UM)
  ◦ Extensive, or normal, metabolizer (EM)
  ◦ Intermediate metabolizer (IM)
  ◦ Poor metabolizer (PM)
• 5-14% of Caucasians, 0-5% Africans, and 0-1% of Asians classified as PM
• 4-6% of Caucasians, 3-6% of African-Americans and 2% of Asian-Americans classified as UM

Spectrum of Metabolism/Analgesia

At extreme ends → Clinical problems with the use of codeine and potentially with other opioids metabolized by CYP2D6: tramadol, oxycodone and hydrocodone
Opioid-Induced Respiratory Depression in Paediatrics: A Review of Case Reports

- PubMed as of 2012: 27 cases of opioid-induced respiratory depression (OIRD) described in 24 reports
  - Seven cases were fatal
  - In eight cases, OIRD was due to an iatrogenic overdose
- Three distinct patterns related to OIRD include:
  1. Morphine administration in patients with renal impairment, causing accumulation of its active metabolite
  2. Codeine use in patients with CYP2D6 ultra-rapid metabolizer phenotype, causing enhanced morphine production
  3. Opioid use in patients after adenotonsillectomy for recurrent tonsillitis and/or obstructive sleep apnea, where OIRD may be related to hypoxia-induced enhancement of OIRD


Is It Farewell to Codeine?

- “Codeine is just not that good an analgesic.”
- Single 60 mg dose codeine → NNT of 12 for adult pain.
- Analgesia may be mediated through morphine but codeine receptor occupancy contributes to side effects

[U.S. FDA Black Box Warning] (2-20-2013)
- “Health care professionals should prescribe an alternate analgesic for post-operative pain control in children who are undergoing tonsillectomy and/or adenoidectomy. Codeine should not be used for pain in children following these procedures. For management of other types of pain in children, codeine should only be used if the benefits are anticipated to outweigh the risks.”


Oral Opioids for Pediatric Pain in 2015

- There is no role for codeine and very little role for hydrocodone in pediatric acute or chronic pain

- **Oxycodone**
  - 5 mg capsules or 5, 10 mg tablets or 5 mg/5 ml liquid
  - NOT 20 mg/1 ml liquid for adult cancer patients
  - Pediatric dose = 0.1 mg/kg PO q 4-6 hrs PRN

- **Hydromorphone**
  - 2 mg hydromorphone = 5 mg of oxycodone
  - 2, 4, 8 mg tablets or 1 mg/1 ml liquid
  - Pediatric dose = 0.03 – 0.08 mg/kg PO q 4-6 hrs PRN

- **Oxymorphone** – Likely ideal PK, **but nil pediatric data**
  - 5 mg oxymorphone = 10 mg oxycodone
  - 5, 10 mg IR tablets; no oral liquid preparation
Barriers to Optimal Postoperative Analgesia at Home

<table>
<thead>
<tr>
<th>Inadequate Prescription</th>
<th>Medication Factors</th>
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<tr>
<td></td>
<td>Inadequate strength</td>
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<td>Inappropriate type/class</td>
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<td>Adverse effects</td>
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<td>System Factors</td>
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<td>Lack of adequate discharge information</td>
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<td>Poor health provider communication</td>
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<td>Access to analgesics</td>
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<td>Inadequate Administration</td>
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<td>Parental Factors</td>
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<td>Attitudes and misconceptions</td>
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<td>Knowledge deficits</td>
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<td>Poor assessment of pain</td>
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<td>Sociodemographics and culture</td>
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<td>Child Factors</td>
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<td>Refusal to take medication</td>
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<td>Varied expression of pain</td>
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<td>High anxiety levels</td>
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A Paradigm Shift to Balance Safety and Quality in Pediatric Pain Management

- Multidisciplinary group convened for a 3-day workshop to create a reliable method for preoperative discussion of the pain plan for ambulatory hernia repair
- Adoption of continuous performance improvement (CPI), based on the iterative Toyota Production System (TPS)
- Four objectives were defined:
  1. Pain management is discussed by the provider with parent
  2. Pain plan is accurately documented in the EMR
  3. Parents perceive that pain is adequately discussed
  4. Behavioral indicators demonstrate the pain plan is effective


A Paradigm Shift to Balance Safety and Quality in Pediatric Pain Management

- 235 hernia repair patients enrolled over 240 day period
- Compliance with targets
  - 87-100%
  - 80%
  - 73%
  - Pain score of ≤ 6 of 15 was adequately controlled in all patients whose parent was contacted by telephone (N = 113).

*Parent’s Postoperative Pain Measure: validated behavioral pain measure


- "Balancing the potential harm from undertreating pain and inappropriate use of opioids requires an evidence-based, multidisciplinary family-centered approach."

- "The development and implementation of a reliable method for the management and treatment of pain reduces variability allowing for delivery of safe and quality care."


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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>13.5 years</td>
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<tr>
<td>Gender</td>
<td>71% female</td>
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<tr>
<td>Race</td>
<td>79% White/not Hispanic or Latino</td>
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<tr>
<td>Length of Stay</td>
<td>7.32 days</td>
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<td>Readmission Rate with 1 year</td>
<td>13%</td>
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<tr>
<td>Mean Number of Diagnoses</td>
<td>10</td>
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<tr>
<td>Most Common Admission Diagnoses</td>
<td>Abdominal pain (23%), RSD (9%), Headaches/migraines (5%), Limb/extremity pain (5%), Back pain/lumbago (3%)</td>
</tr>
<tr>
<td>Most Common Pain Diagnoses</td>
<td>Chronic pain/chronic pain syndrome (65%), RSD (26%), Psychogenic pain (22%)</td>
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<tr>
<td>Psychiatric Diagnosis</td>
<td>44%</td>
</tr>
</tbody>
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Pediatric Health Information System (PHIS); 2004-2010; N = 3752

Pain Prevalence and Trajectories Following Pediatric Spinal Fusion Surgery

- Scoliosis Research Society Questionnaire Version 30
  - Pain, activity, mental health, and self-image subscales
- 190 patients prior to surgery and at 1 and 2 years post-surgery
- 77 provided 5-year post-surgery data

Prevalence of Moderate to Severe Pain: 11% at 1 year post-surgery, 15% at 2 years post-surgery, and 15% at 5 years post-surgery


- Scoliosis Research Society Questionnaire Version 30
- 190 patients prior to surgery and at 1 and 2 years post-surgery
- 77 provided 5-year post-surgery data


Pediatric Chronic Post-Surgical Pain

- 113 patients – 51% orthopedic procedures
- 13% experienced chronic postoperative pain
- Median duration of 4.1 months – 23% “Everyday”
- Chronic pain-related interference of function:
  - Extracurricular activities (31%), sleep (31%), school (15%)
- “Given the large number of children at risk for experiencing chronic postoperative pain, preventative efforts are necessary.”
- “Large-scale cohort prospective studies are needed to confirm the results of this cross-sectional study.”


The number of children admitted with chronic pain increased by 831% from 2004 to 2010.

The Heart of the Child

“The mystical heart of a child is a precious and beautiful thing. It is marred only by wounds of a thoughtless and not too intelligent world...

In an emotional sense it is susceptible to wounds of indifference, thoughtlessness and neglect, and during episodes of illness is particularly vulnerable...

I am convinced that the heart of a child sunned by love, security and understanding will be able to withstand the storms of illness and pain.”

Willis J. Potts, M.D., Surgeon-in-Chief, Children’s Memorial Hospital, 1959