Treating and Preventing Acute, Procedural, and Chronic Pain in Infants, Children and Teenagers

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Associate Professor of Pediatrics, University of Minnesota Medical School

Disclosure
• The views presented in this lecture are my own. NO conflict of interest exists with my presentation
• I do not intend to discuss unapproved or investigative use of commercial products or devices (= off-label).
• Current Research Support: NIH/NCI [1R25CA151000-01]; Internal Research Grants Program (IRGP) Children's of MN

Pain after burn injury: Multifactorial
- Acute pain
  - Tissue damage, repetitive trauma
- Procedural pain
  - Dressing changes, intravenous access
- Neuropathic pain
  - Post-inflammation pain, post-injury pain
- Psycho-spiritual-spiritual pain
- Chronic pain
- Pain can persist after healing

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Today’s Presentation
- Part 1: Acute Pain
- Part 2: Procedural Pain
- Part 3: Neuropathic Pain

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

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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

Inappropriate Analgesia: Why Bother...

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression
- Inadequate analgesia for initial procedures in children diminishes effect of adequate analgesia in subsequent procedures
- NICU: increased morbidity & mortality
- Children (n=48) with injury that led to hospital treatment: morphine was associated with lower levels of PTSD follow-up 6 months later
- 6-16 year-olds (n=24) with acute burns: Children receiving higher doses of morphine had greater reduction in PTSD symptoms over 6 months
- 12- to 48-month-old (n=70) children with acute burns admitted to major pediatric burn center: Management of pain with higher doses of morphine associated with decreasing number of symptoms of PTSD in months after major trauma
- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression

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! (compartment syndrome?)... analgesia second...

Trauma & post-traumatic stress disorder (PTSD)

- Children (n=48) with injury that led to hospital treatment: morphine was associated with lower levels of PTSD follow-up 6 months later
- 6-16 year-olds (n=24) with acute burns: Children receiving higher doses of morphine had greater reduction in PTSD symptoms over 6 months
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Myths and Barriers to Using Opioids

Case Scenario:
- You are taking care of a child with severe acute somatic nociceptive pain caused by major burn… It crosses your mind to administer a strong opioid such as morphine or fentanyl
- What would be the most common concerns you might hear from your colleagues or parents arguing against opioid use in this child?

Safety of Analgesics

“Dr. Cox, I am worried about drug safety… would it be okay not using analgesia for children in acute pain?”
Opioid Safety & Long-Term Outcome


- Continuous morphine infusion of 10 mcg/kg/h during the neonatal period does not harm general functioning and may even have a positive influence on executive functions at 8 to 9 years. (MacGregor R, Evans D, Sugden D, Gaussen T, Levene M. Outcome at 5-6 years of prematurely born children who received morphine as neonates. Archives of disease in childhood Fetal and neonatal edition. 1998 Jul;79(1):F40-3.)


Does analgesia improve outcome?

- Yes, in animal model. (Suellen Walker, PhD, London)

How Do We Manage Acute Pain in Children?
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 ("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 American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain 2008. 24-27

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

Switching Opioids

Differences between opioids in the balance between analgesic cross-tolerance level and the level of cross-tolerance to adverse effects can be exploited to clinical advantage.

Switching opioids can possibly achieve a more favorable balance between analgesia and adverse effects, hence the rationale for trial of a different opioid in the event of toxicity or inadequate analgesia.


Regular (!) Pain Assessment

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

Pain in children with impaired communication

- Non-communicating Children's Pain Checklist - Revised (NCCPC-R); postoperative Version (NCCPC-PV) (Breau, 2002)
- Pediatric Pain Profile (PPP) (Hunt, 2003)
- r-FLACC (Malviya 2006)
**Route of Administration**

- **oral**
- **i.v./s.c.**
- **intranasal (MAD device)**
- **intramucosal**
- **transdermal**
- **sublingual**
- **suppository**

**Analgesic Medications**

**Nociceptive Pathways & Primary Sites of Action of Analgesics**

1. **Injury**
2. **Thalamus**
3. **NSAIDs**
4. **Acetaminophen (Paracetamol)**

**WHO Principle 4:** 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**

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

**Non-Opioids**

- Acetaminophen / Paracetamol
- NSAIDs

**4 WHO-Principles**

- "By the clock"

**Multimodal (Opioid-sparing) Analgesia**

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

- **Non-Opioids**
  - Acetaminophen / Paracetamol
  - NSAIDs

**Integrative Therapies**

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

**Citius, Altius, Fortius...?**

- Ibuprofen salts: fast-acting formulations
  - Advil® Film-Coated Tablets, contains 266 mg of ibuprofen sodium (equivalent to 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? Peloso, P.M., Faster, higher, stronger: to the gold medal podium? Pain, 2014. 155(1): p. 4-5.

**WHO Step 2**

**Moderate to Severe Pain**

- Morphine
  - or fentanyl, hydromorphone, oxycodone, methadone (UK: diamorphine)
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

A Pediatrician’s Top 10 Apps for Distraction & Pain Management http://NoNeedlessPain.org

Integrative Pain & Symptom Management

Nociceptive Pathways & Primary Sites of Action of Analgesics

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

Multimodal Analgesia

- 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
Today’s Presentation

- Part 1: Acute Pain
- Part 2: Procedural Pain
- Part 3: Neuropathic Pain

Procedural Pain: From IV access, lab draws to dressing change

Don't have enough staff for pediatric pain control...

Funny, how there is always enough staff to restrain a child.

What are children most afraid of when coming to see a doctor?

Needle Pain: A Call for Action

- Needle procedures (incl. vaccine injections) performed in childhood are a substantial source of distress
- By age 2: 14-20 vaccine injections in US
- Children get behind in vaccination schedule

It is estimated that up to 25% of adults have a fear of needles


Procedural pain: A Call for Action

- Pain ratings at 4-6 months routine vaccination higher for uncircumcised versus circumcised boys Taddio A (1994) Lancet, 344:291-2
- Memory of previous painful experience has great influence on pain experience during subsequent procedures
- Inadequate analgesia for initial procedures in young children (8 years or younger) diminishes the effect of adequate analgesia in subsequent procedures

What do we need to do?
“Hey, it is not rocket surgery”

Joey Tribbiani, Friends

“Non-negotiable” Components of Needle Pain Prevention

- “Non-Negotiable”
  - Topical Anesthesia
  - 0-12 months: Sucrose
  - Positioning
  - Distraction (Integrative “non-pharmacological” therapies)

- Develop Plan B (or deferral process)
  - Nitrous gas sedation
  - Consider moderate-deep sedation, if excellent analgesia cannot be achieved
  - Possibly other approaches

Children's Minnesota

We will do everything possible to prevent and treat pain.

Alex & Danielle
Children's patients

Essential Components of Needle Pain Prevention

1. Numb the skin
2. Sugar water or breastfeeding for babies
3. Comfort positioning
4. Distraction

4 steps to make needles less painful

1. Numb the skin
2. Sugar water or breastfeeding for babies
3. Comfort positioning
4. Distraction

Watch videos at childrensMN.org/comfortpromise.

We aim to make needles less painful.
Topical local anesthetic use on burn wound is controversial

- Prilocaine-lidocaine cream (EMLA) has no effect on burn pain in volunteers
- EMLA reduces duration of erythema after mild thermal injury; suggests a potential use in clinical practice in the treatment of minor skin burns
- Prilocaine-lidocaine cream (EMLA) reduces duration of erythema after mild thermal injury; suggests a potential use in clinical practice in the treatment of minor skin burns
- Topical lidocaine is significantly tempered by reports of local anesthetic-induced seizures due to enhanced systemic absorption at the open wound site
- Dressing changes of partial thickness skin graft donor sites: lidocaine vs xylocaine formulations achieved low pain scores during dressing changes
- Topical lidocaine use is controversial

Topical Opioids for Wounds

- Topical (not intended) review: Topical opioids are clinically useful and safe for controlling inflammatory pain in wounds
- Opioid receptors: peripheral nerves, inflamed tissue
- Probably no systemic effect with topical morphine administration
- Animal studies: opioids can accelerate wound healing (by upregulating nitric-oxide synthase)

- 3 RCTs, n=34 adults => effective; 1 RCT, n=18 => no effect
- Adults: Mixture morphine 10mg/mL injection in 8 gram of Intrastite gel: cover wound (5-10 mL) x1-3/day

Topical Local Anesthetics for Needle Pain

- Topical lidocaine use is significantly tempered by reports of local anesthetic-induced seizures due to enhanced systemic absorption at the open wound site
- Topical lidocaine is significantly tempered by reports of local anesthetic-induced seizures due to enhanced systemic absorption at the open wound site
- EMLA 1-2 hours vs. LMX 1 hour
- For children undergoing vaccination, there is insufficient evidence for or against the use of skin-cooling techniques (vapocoolants, ice, cool/cold packs) to reduce pain at the time of injection (grade I recommendation, based on conflicting level I evidence).

EMLA versus LMX

- EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) vs Ela-Max LMX 4% Lidocaine Topical Anesthetic Cream (1) Koh JL, Harrison G, Miyas B, Smith PA. Double-blind comparison study of EMLA and EMLA LMX 4% lidocaine topical anesthetic cream for pain control during the local anaesthetic injection. Pediatrics. 2003 Apr;111(4):E33. 
- EMLA application for preventing pain during IV insertion in Children
- Analgesia duration:
- EMLA 1-2 hours vs. LMX 1 hour
- Skin time:
- EMLA 4 hours vs. LMX 2 hours
- EMLA versus LMX

Success of venipuncture or venous cannulation in children

- 388 children (255 with EMLA, 133 without). Procedures were successful at first attempt
- EMLA application for preventing pain during IV insertion in Children
- Analgesia duration:
- EMLA 1-2 hours vs. LMX 1 hour
- Skin time:
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- Cellophane (no Tequaderm: might hurt at time of removal)

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**J-Tip (Lidocaine)**

- J-tip: single-use, disposable, carbon-dioxide-powered, needle-less lidocaine injector

---

**Non-negotiable** Components of Needle Pain Prevention in Children

1. J-Tip (Lidocaine)
2. Sucrose
3. Positioning
4. Distraction

---

**Sucrose for Children 0-12 months**

- Reduces pain (PIPP, VAS) and cry during painful procedure, such as venipuncture
- Role of endogenous opioids - naloxone blunts effect
- Effective dose (24%): 0.05 - 0.5 mL (= 0.012 - 0.12 g)
- Administration 2 minutes prior to mild - moderately painful procedure
- Duration ~ 4 min
- Does not prevent development of hyperalgesia?

- Breastfeeding
  - Effective in term infants (superior to sweetening agents)
  - Ineffective in preterm infants

---

**Breastfeeding effectively reduces procedural pain**


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**“Non-negotiable” Components of Needle Pain Prevention in Children**

3. Positioning

“Non-negotiable” Components of Needle Pain Prevention in Children

3. Positioning

- When feasible, offer choice to child (parent’s lap?)
  *Parents are not “partners in crime”

Positioning

Comfort positions for needle procedures

- Babies (0-12 months)
  - Held by parent
  - Swaddled or skin to skin
  - Pacifier with sugar water or breastfeeding
  - Distraction: favorite toy, blanket or music
- Toddlers and preschoolers (1-5 years)
  - Held by parent, sitting upright is best
  - Distraction: bubbles, books, toys or music
- School age (6-12 years)
  - Held by parents or close by, upright is best
  - Distraction: interactive toys, books or electronics
  - Child may choose to watch or lay down
- Teens (13-18 years)
  - Parents available
  - Sitting upright is best
  - Distraction: interactive toys, books or electronics
  - Teen may choose to watch or lay down

Swaddling, facilitated tucking, kangaroo care
“Non-negotiable” Components of Needle Pain Prevention in Children

4 simple steps to reduce needle pain

4. Distraction

With quote from phlebotomist

Integrative Therapies for Needle Procedures


• There is strong evidence that distraction and hypnosis are effective in reducing the pain and distress that children and adolescents experience during needle procedures

• Promising but limited/no evidence for preparation and information or both, combined CBT, parent coaching plus distraction, suggestion, or virtual reality

Integrative Therapies for Needle Procedures

• To reduce pain at the time of injection among children four years of age and older, offer to rub or stroke the skin near injection site with moderate intensity before and during vaccination (grade B recommendation, based on level II-1 evidence) Taddio A, Appleton M, Bortolussi R, Chambers C, Dubey V, Halperin SA, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline. CMAJ: Canadian Medical Association journal 2010 Dec 14;182(18):E843-55.

• Parent coaching: Certain types of parental behaviours (e.g., nonprocedural talk, suggestions on how to cope, humour) have been related to decreases in children’s distress and pain, whereas others (e.g., reassurance, apologies) have been related to increases in children’s distress and pain Taddio A, Chambers C, Halperin SA, et al. Inadequate pain management during childhood immunizations: the nerve of it. Clin Ther 2009;31(Suppl 2):S152-67.

Distraction

Hypnosis in Pediatric Practice: Imaginative Medicine in Action

By Laurence Sugarman, MD

A documentary for child health professionals
Distraction

• Reduction of fear and anxiety
• Determine if the child wishes to watch or be distracted
• Young children: books, bubbles and pinwheels
• Coaching roles for parents
• Older children: video games and biofeedback

What’s Plan B?

If good procedural analgesia not feasible with the “4 Non-Negotiables”, refer patient to:
1. Child Life (they really should have been involved by now)
2. Needle Phobia: psychology (CBT)
3. Mild sedation: Nitrous gas
4. Moderate/deep sedation (e.g. ketamine, propofol)

Note:
A sedative alone (such as a benzodiazepine) can never be a substitute for procedural analgesia.

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• Part 1: Acute Pain
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• Part 3: Neuropathic Pain

Pain after burn injury

• Multi-factorial involving tissue damage, repetitive trauma and damage to sensory nerve endings

• Neuropathic pain component

• Pain can persist after healing

Neuropathic Pain Assessment

Thank you Patricia D. Scherrer MD, Medical Director, Sedation Services
Children’s Hospitals and Clinics of Minnesota

To day’s Presentation

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• Part 2: Procedural Pain
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Neuropathic Pain Assessment

Big Hero 6 (2014)
Neuropathic Pain Assessment

- Currently there are no validated neuropathic pain scales for children < 18 years
- **Adults**
  - NPS® Neuropathic Pain Scale - 12 items
  - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm)

  - **Pain Quality Assessment Scale (PQAS) - 20 items**
  - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm)

Medication (number of placebo-controlled studies)

<table>
<thead>
<tr>
<th>Medication (class)</th>
<th># of participants</th>
<th>Pain Relief</th>
<th>Placebo NNT</th>
<th>NNH</th>
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<tr>
<td>Botox A (4)</td>
<td>137</td>
<td>60%</td>
<td>6%</td>
<td>1.9 ns</td>
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<tr>
<td>TCAs (15)</td>
<td>948</td>
<td>45.9%</td>
<td>17.9%</td>
<td>3.6 13.4</td>
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<td>Strong Opioids (7)</td>
<td>838</td>
<td>51.9%</td>
<td>26.2%</td>
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<tr>
<td>Tramadol (6)</td>
<td>741</td>
<td>46.3%</td>
<td>26.6%</td>
<td>4.7 12.6</td>
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<tr>
<td>Gabapentin (10)</td>
<td>3503</td>
<td>34.7%</td>
<td>20.3%</td>
<td>4.3 12.4</td>
</tr>
<tr>
<td>Serotonin-noradrenaline reuptake inhibitor (10)</td>
<td>2541</td>
<td>43.4%</td>
<td>28.3%</td>
<td>6.4 11.8</td>
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<tr>
<td>Pregabalin (25)</td>
<td>5940</td>
<td>38.5%</td>
<td>24%</td>
<td>7.7 13.9</td>
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<tr>
<td>Capsaicin 8% (6)</td>
<td>2073</td>
<td>35.9%</td>
<td>27.4%</td>
<td>10.6 ns</td>
</tr>
</tbody>
</table>

* extended release gabapentin NNT: 8; NNH 21.9 (p<0.05)

- Pain Quality Assessment Scale (PQAS) - 20 items
- [http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm)

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. Identify and treat underlying disease process (radiation?) (corticosteroids?)

NSAIDs for Neuropathic Pain

- NSAIDs are so widely viewed as being ineffective for neuropathic pain that no major guidelines even mention them in their algorithm, and no Cochrane or NICE ormanaged care organizations recommend them. The Lancet. Neurology. Feb 2015;14(2):162-173.

Opioids for Neuropathic Pain

**“Weak” opioids (multimechanism)**

- No additional benefit > 180 mg morphine equivalent
- Cochrane analysis: Oxycodone NOT effective as a pain medicine in diabetic neuropathy or postherpetic neuralgia.

**“Strong” Opioids**

- Tapentadol! Bias; NNT 10.2
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

Tricyclic antidepressants (TCA)
- Secondary amine TCAs (nortriptyline and desipramine) better tolerated than tertiary amine TCAs (amitriptyline and imipramine) with comparable analgesic efficacy.

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

Nociceptive Pathways & Primary Sites of Action of Analgesics

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

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

Gabapentinoids: Ca-channel α2-δ ligands
- Voltage-gated Ca-channel
- α2-δ subunit (dysfunction/upregulation role in neuropathic pain)

Presynaptic nerve terminal
Postsynaptic nerve terminal

Glutamate
Substance P
Gabapentin

- 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 3.9

Pediatric Dosage
- Gradually increasing from 3-5 mg/kg/dose TID to 10-20mg/kg/dose TID, max. 1,200 mg/dose TID
- Infants: 4.5 mg PO Q6h (titrated to max. 15 mg Q6h)
- Extended release: 300 -> 1800 mg Qday: No pediatric data; NNT worse
- 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)

Pregabalin

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

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Thalamus

NSAIDs

Acetaminophen (Paracetamol)

2nd Neuron

Periaqueductal grey (endorphins)

Descending Inhibition

+ Integrative (non-pharmacological) therapies

Combination: Amitriptyline & Gabapentin

Opioids

Inhibitors of excitatory glutamate systems:

Gabapentin/Pregabalin

Carbamazepine*

Valproate

Combination:

Amitriptyline & Gabapentin

Management of Neuropathic Pain in Pediatrics

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(1) Identify and treat underlying disease process (radiation?)
(2) Regional anesthesia, if appropriate
(3) Integrative therapies & Rehabilitation manage comorbidities (anxiety, sleep disturbances), Psychological Therapies.
(4) NEW (1) onset: Opioid analogues [consider Tramadol or Methadone] plus NSAID
(5) Tricyclic Antidepressant and gabapentinoid
(6) Tricyclic Antidepressant (or gabapentinoid) + low-dose ketamine
(7) Lidocaine patch (if localized pain).

Example:

| 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)

Topical Lidocaine 5% patch

- RCT n=87 effective adjunct in post-operative (knee replacement) pain management
- 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?]

Example: 10-year-old girl, 30 kg

- Lidocaine patch

For localized pain only

- Patch can be cut to fit
- 12 hours on/12 hours off [possibly longer?]
### Management of Neuropathic Pain in Pediatrics

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Intervention</th>
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| 1.    | **Nausea after 4 days?**  
Neuropathic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mg/kg/hr | |
| 2.    | **Side Effects:**  
- Allergic reaction  
- Nausea after 4 days?  
- Disturbances) Psychological Therapies. | |
| 3.    | **Case Series** (n=5) after anti-GD2 antibody therapy in children with neuroblastoma: 1mg/kg/hr - Infusion 1 mg/kg over 5 min, then 1mg/hr - target: 2-5 mg/kg/hr. Intravenous lidocaine effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma, in report of 2 patients. | |
| 4.    | **Case report:**  
| 5.    | **Case report:**  
- 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain. IV Lidocaine (9.3-14 mg/kg/hr) - (Pediatr Neurol 2013 Jul;59(2):179-82). | |
| 6.    | **Oral Mexiletine, Tocaainde, Flecainide:**  
High side effect liability from oral drugs. Not recommended | |

### IV Lidocaine - Pediatric Experience

- **Nausea after 4 days?**  
Neuropathic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mg/kg/hr. (Lancet 1987; 1:96).  
**Side Effects:**  
- Allergic reaction  
- Nausea after 4 days?  
- Disturbances Psychological Therapies. | |

### Other Sodium Channel Blocker

- **How about local lidocaine and novocain?** | |

### Cannabis

- **Cannabinoids:**  
- NNH 12.1  
- Only 2 out of 9 trials positive  
- RCT Cancer pain: not effective  
- RCT Cancer pain: not effective  
- **Cannabidiol (CBD):**  
- Effective for MS patients with neuropathic pain | |

### Cannabis

- **Correlation with mental illness**  
Cannabis use has been associated with the development of mental illness. There is a significant correlation between cannabis use and the development of mental illness among adolescents and young adults. However, the specific mechanisms by which cannabis use contributes to mental illness are complex and not fully understood. | |
- **Impacts on work**  
Health issues associated with cannabis | |
- **3 studies show positive correlation**  
between marijuana use and testicular cancer  
- **Fluffy, should we use cannabis in children?** | |
Early-Onset, Regular Cannabis Use Is Linked to IQ Decline

• Study participants who initiated weekly cannabis use before age 18 dropped IQ points in proportion to how long they persisted in using the drug, while nonusers gained a fraction of a point.


Positive Effects

Cannabinoids
• May result in reduction of pain and inflammation
• May work as an antiepileptic

Negative Effects

Cannabinoids
• Youthful exposure leads to earlier onset & more severe psychosis, incl. schizophrenia
• 9% of adults (17% teens) who experiment with marijuana become dependent
• Samples from household marijuana grew up to 10,000,000/gram organisms Salmonella muenchen (incl. 85 cases of acquired enteritis in Georgia, Alabama, Ohio, Michigan)

Botulinum toxin A
• Peripheral neuropathic pain
• 6 RCTs: 50-200 units s.c. in the region of pain
• Low placebo effect

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
http://aapnews.aappublications.org/content/early/2015/01/26/aapnews.20150126-1
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


LET Anesthesia
- Sitting upright
- Distraction
- Topical Anesthesia
  - 3mL LETgel: Lidocaine 4% - Epinephrine 0.18% - Tetracaine 0.5%


Conclusions
- Withholding evidence-based analgesia to hospitalized infants / children in pain 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
- 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
- Patients/Parents do NOT have to choose between poor pain control or over sedation

Opioids should NOT be administered long-term
Opioids NOT indicated for chronic pain
Treatment protocol for painful procedures is expected standard of care in 21st century:
  - positioning, topical anesthesia, integrative therapies, sucrose
  - plus/minus sedation; systemic anesthesia
Neuropathic pain often under-assessed and under-treated
Careful step-by-step approach (combining integrative, rehabilitative, pharmacological and interventional therapies) warranted
  - First Line medications: Opioids (?), Amitriptyline, Gabapentin
  - Low-dose Ketamine may represent a potent adjunct analgesia

With profound gratitude to our interdisciplinary Pain, Palliative & Integrative Medicine team

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Further Training:
CIPPC@ChildrensMN.org

9th Annual Pediatric Pain Master Class
* Minneapolis, MN | June 11-17, 2016 http://www.cvent.com/d/kfo8an

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer

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