The Management of Neuropathic Pain and the Use of Adjuvant Analgesia

Stefan J. Friedrichsdorf, MD, FAAP
Medical Director, Department of Pain Medicine, Palliative Care & Integrative Medicine, Children's Hospitals and Clinics of Minnesota, Minneapolis/St. Paul, MN
Associate Professor of Pediatrics, University of Minnesota Medical School

- Appreciate high prevalence of neuropathic pain in patients with serious illnesses
- Define neuropathic pain and describe main causes
- Develop a step-by-step treatment approach for neuropathic pain
How Do We Manage Acute Pain in Children?

No Needless Pain
That’s why we’re called

No Needless Pain
Multimodal Analgesia

(WHO)-Principles of Pediatric Acute Pain Management

- 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”)

.connector
Regular (!) Pain Assessment

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

<table>
<thead>
<tr>
<th>Infant FLACC Scale</th>
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<tr>
<td>Category</td>
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<td>Pain</td>
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<tr>
<td>Respiration</td>
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<td>Activity</td>
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<td>Sleep</td>
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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)

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

- Intravenous (i.v. / s.c.)
- Intramuscular (i.m.)
- Oral
- Intranasal (MAD device)
- Transdermal
- Suppository
- Transmucosal
- Sublingual
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

- Morphine
- or fentanyl, hydromorphone, oxycodone, methadone

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**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...?
  - Rats not before P7 to P21, i.e. 4-5 months in children...
  - Damage early on: no memory...adaptive immune system...?

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
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
  - Pain Quality Assessment Scale (PQAS) - 20 items
    - http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm
- Patients simultaneously may experience different qualities, including
  - Nociceptive Pain
    - Somatic Pain
    - Visceral Pain
  - Psycho-social-spiritual Pain (“Total Pain”)
  - and/or Neuropathic Pain
- Be creative when measuring pain: a single pain score often will not be enough:

Pinky speaks for Nadia

Pain Assessment
Case Report: Clark

- 15-year-old, relapsed T-cell lymphoma, weight: 72 kgs
- Onset of chemotherapy-induced bi-pedal neuropathy VAS 9/10
- Abdominal pain (hemorrhagic cystitis)
- Unresponsiveness versus over sedation
- Autonomic changes at feet

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Acetaminophen (Paracetamol)

NSAIDs
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.


- Preclinical and clinical studies have demonstrated efficacy for NSAIDs in neuropathic pain states.


- NSAIDs are commonly prescribed for neuropathic pain.


WHO Principle:
Using a Two-Step Strategy

WHO Step 1
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- and/or
- Acetaminophen (Paracetamol)

Other NSAIDs? COX-2 Inhibitor?

WHO Step 2
Moderate to Severe Pain

- Morphine
- or fentanyl,
- hydromorphone,
- oxycodone,
- methadone

Opioids for Neuropathic Pain

- Adult Evidence: Metaanalysis: Opioids, including tramadol, have a consistent efficacy in neuropathic pain.


- Multi-mechanism agent

- Strong opioids: RCTs: efficacious for neuropathic pain (NP), including phantom limb pain, chronic peripheral and central NP.

Case Example: Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

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

WHO-Principles
- "By the clock"
- "By the child"
- "By the appropriate route"
- "By the WHO ladder"

COX-2-INHIBITOR:
Celecoxib 200 mg BID

OPIOID:
Hydromorphone PCA 1.35 mg/hr (max. 52 boluses/day [1.35mg])

Rotation: Methadone
30 mg/day [5 mg IV Q4h -> 10 mg IV Q8h] plus Hydromorphone
PCA bolus 2mg IV, lockout 10 minutes

PO 10 mg TID -> 12.5 mg TID

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Thalamus

Opioids
- Pre-synaptic nerve terminal
• Neurotransmitter release
- Post-synaptic nerve terminal:
• Membrane hyperpolarization
• suppress neuronal excitability

Acetaminophen (Paracetamol)

NSAIDs

Integrative Therapies
- Massage
- Heat/cold
- Deep Breathing
- Biofeedback
- Hypnosis
- etc.
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)
  - **Behavioral** (deep breathing, imagery, hypnosis, smartphone/tablet “apps”)
  - Acupressure, acupuncture, aromatherapy

Case Report: Clark

- Integrative & supportive therapies
- Behavioral Therapies
  - Breathing
  - Imagery
  - Hypnosis
- Individual Psychotherapy
- Physical Modalities
  - TENS
  - Physical Therapy
  - Stockings
  - Make-a-wish

Nociceptive Pathways & Primary Sites of Action of Analgesics

Descending pathways that modulate transmission of nociceptive signals originate in periaqueductal gray, locus coeruleus, anterior cingulate gyrus, amygdala & hypothalamus: are relayed through brainstem nuclei in the PAG and medulla to spinal cord.

Inhibitory transmitters involved in these pathways incl. norepinephrine, 5-hydroxytryptamine, dopamine, & endogenous opioids.
Case Example: Multimodal (Opioid-sparing) Analgesia

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

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

**WHO-Principles**
- "By the clock"
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**Integrative Therapies**
- Massage
- Heat/cold
- Deep Breathing
- Biofeedback
- Hypnosis
- etc.

**Adjuvants**
- Alpha-Agonists
- Anticonvulsants
- TCA/Antidepressants
- Na-receptor-channel blockers
- NMDA-receptor-channel blockers
- Antispasmodics
- Benzodiazepines
- Muscle relaxants
- Radiopharmaceuticals
- Biophosphonates
- etc.

**WHO-Principles**
- "By the clock"
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**Case Report: Clark**

1. **TRICYCLIC ANTIDEPRESSANT**
   - Amitriptyline 25 mg -> 50 mg QHS
   - Ca-channel α2-δ ligand
     - Pregabalin 50 mg QHS -> 300 mg BID
   - CORTICOSTEROID
     - Dexamethasone 10 mg BID
   - LIDOCAINE
     - 5% patches Q12h on/off

**Tricyclic antidepressants (TCA)**

- 61 RCTs (20 antidepressants): TCAs are effective; NNT of 3.6 (for the achievement of at least moderate pain relief).
- No effect of amitriptyline in HIV neuropathy.
- Secondary amine TCAs (e.g., nortriptyline) better tolerated than tertiary amine TCAs (e.g., amitriptyline) with comparable analgesic efficacy.

**No effect in chemotherapy-induced neuropathy**
**Amitriptyline**

- **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

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

- Thalamus
- Periaqueductal grey (endorphins)
- Opioids
- Acetaminophen (Paracetamol)
- NSAIDs
- Tricyclic Antidepressants: (+) Opioid analgesia via serotoninergic mechanism at brainstem
- Integrative (non-pharmacological) therapies
- TCA SSRIs Methadone Tramadol
- Descending Inhibition
- Integrative (non-pharmacological) therapies

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**Case Report: Clark**

- **(1) TRICYCLIC ANTIDEPRESSANT**
  - Amitriptyline 25 mg -> 50 mg QHS
- **(2) Ca-channel α2-δ ligand**
  - Pregabalin 50 mg QHS -> 300 mg BID
- **(3) CORTICOSTEROID**
  - Dexamethasone 10 mg BID
- **(4) LIDOCAINE**
  - 5% patches Q12h on/off
**Gabapentinoids: Ca-channel α2-δ ligands**

- **Gabapentin:** 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

- **Pregabalin:** Effective in post herpetic neuralgia, painful diabetic polyneuropathy, central neuropathic pain (19 studies, 7003 participants); effective 300 mg-600 mg daily (at 150 mg daily was generally ineffective).
  - No overall evidence for superior efficacy for either of these drugs in neuropathic pain, although lower cost may favor gabapentin

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

- **Gabapentin/Pregabalin**
- **Carbamazepine**
- **Valproate**
- **Combination:** Amitriptyline & Gabapentin
- **TCA & Methadone & Tramadol**
- **SSRIs**
- **Acetaminophen (Paracetamol)**
- **Opioids**
- **NSAIDs**

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**Presynaptic nerve terminal**

- Glutamate
- Substance P

**Postsynaptic nerve terminal**

**Voltage-gated Ca-channel**

**α2-δ subunit**

[Dysfunction/upregulation role in neuropathic pain]
**Sodium Channel Blocker: Topical Lidocaine**

- **Lidocaine (systemic or local):** Decrease of neuropathic pain related to decrease of ectopic ongoing activity in injured afferent nerve fibers. 

- **Topical Lidocaine 5% patch (Lidoderm®, generic available).** Metaanalysis: Data is conflicting. 

- **Efficacy of IV lidocaine supported by RCTs**

**IV Lidocaine - Pediatric Experience**

- **Nausea after 4 days?**
  - Neoplastic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mcg/mL. 

- **Side Effects:** Allergic reaction (serious, but rare), dose related: numbness around mouth, dizziness, slurring of speech, hallucinations, muscle twitches, seizures.
  - R. Pace JA. How to initiate and monitor intravenous lidocaine for severe and/or refractory neuropathic pain. The journal of supportive oncology. 2004 Jan-Feb;[1]:1-8.

- **Case Series (n=5) after anti-GD2 antibody therapy in children with neuroblastoma:**

- **Case report; end-of-life cancer care:**

- **Case report; 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain:**
Opioid induced tolerance and hyperalgesia

- Mu-receptor
- Stimulation
- Genes
- Activation
- Protein Kinase-C
- Other neuromodulators
- Uncoupling
- Inhibition of Ca channels: neurotransmitter release
- Alter neuronal excitability
- Membrane Hyperpolarization (K+ channel)

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NMDA-Receptor Channel Blocker

1. Membrane potential at resting level
   -> channel blocked by Magnesium

Excitatory NMDA (N-Methyl-d-Aspartat) Receptor channel complex
2. Membrane potential changed as a result of ↑ excitation
   - Opioid-sensitivity
     - Central (dorsal horn) sensitization
     - Radiation of pain
     - Spontaneous pain
     - Hyperalgesia, allodynia

3. Phencyclidin (PCP) - binding sites [uncompetitive NMDA receptor antagonists with moderate affinity]
   - Ketamine
   - Methadone
   - Levorphanol
   - (Dextrometorphane?)

**Ketamine**

- **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]
  - Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??
**Ketamine**

- Steady-state oral/parenteral ratio unclear
- Bio-availability 93% IM/IV; 20% PO
- Ketamine -> norketamine
- 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


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**Case Report: Clark**

Subanesthetic-dose Ketamine-PCA

Day 1: 4 mg/hr [0.9 mcg/kg/min] plus 4 mg bolus

↑ 8 mg/hr [1.9 mcg/kg/min] plus 8 mg bolus

Day 2: ↑ 12 mg/hr [2.8 mcg/kg/min] plus 12 mg bolus

Day 3: ↑ 16 mg/hr [3.7 mcg/kg/min] plus 16 mg bolus

Day 5: ↑ 24 mg/hr [5.6 mcg/kg/min] plus 16 mg bolus

Day 8: Change to 40 mg PO PRN

Day 10: 40 mg PO TID [plus 40 mg PRN]

Day 14: Discontinued [changed to PRN only]

* Absent benzodiazepine -> no psychotropic adverse effects

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**Case Report: Clark**

**Number of Hydromorphone PCA Boluses**

55 -> 20/day [↓ 64% over 3 days]

**Opioid Use**

71 mg/day -> 32 mg [↓ 55% over 4 days]

**Pain Score:**

Bolus Response Hydromorphone: VAS 9/10 -> 7/10

Bolus Response Ketamine: VAS 9/10 -> 2/10

Usual Pain Scores: VAS 9/10 -> 2-3/10 [over 4 days]

**Breakthrough Pain**

↓↓↓

**Function**

↑↑
**Case Report: Clark at Home**

**Methadone:** 10 mg PO TID -> 12.5 mg PO TID -> 10 mg PO TID

**Hydromorphone:** 10 mg PO Q1h PRN (0-3/day)

**Pregabalin:** 300 mg BID

**Amitriptyline:** 50 mg QHS

**Ketamine:** 40 mg PO PRN Q1h (discontinued after 2 weeks)

**Lidocaine Patches:** Discontinued after 3 weeks

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**Other Adjuvant Analgesics / Co-analgesics**

- **α-Adrenergic Agonists**
  - (Dexmedetomidine; clonidine)
  - Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory G<sub>i</sub>o-proteins
  - decrease postoperative opioid consumption, pain intensity, and nausea.
  - Recovery times are not prolonged.

- **Capsaicin:** 2 Metaanalyses

- **Benzodiazepines:** gamma-aminobutyric acid (GABA) receptors

- **Capsaicin:** 2 Metaanalyses

- **Sensory-Selective (Nociceptive-Selective) Nerve Blockade**
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- Antispasmodics
- Benzodiazepines
- Corticosteroids
- Muscle relaxants
- Radiotherapeutics
- Biophosphonates
- etc.

**WHO-Principles**
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**Integrative Therapies**
- Massage
- Heat/cold
- Deep Breathing
- Biofeedback
- Hypnosis
- etc.

**Invasive Approaches**
- Regional anesthesia
- Neuraxial anesthesia
- Epidural or intrathecal
- Nerve blocks
- Neurolytic blocks
- [Intraventricular opioids?]
- [Percutaneous cervical cordotomy?]
**Regional anesthesia approaches to pain management in PPC**


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

**Adult Evidence Based Recommendations Neuropathic Pain**

- **First Line**
  - Tricyclic antidepressants & other dual reuptake inhibitors of both serotonin and norepinephrine
  - Ca-channel α2-δ ligands
- **Second Line**
  - Select clinical circumstances: Opioids including tramadol
- **Third Line**
  - Certain antiepileptic and antidepressants, mexiletine, NMDA-receptor antagonists, topical capsaicin

**Management of Neuropathic Pain in Pediatric Palliative Care:**

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

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
2. Integrative therapies; manage comorbidities (anxiety, sleep disturbances)
Management of Neuropathic Pain in Pediatric Palliative Care: Suggested “Non-Evidence-based” Step-by-Step Approach

(8) Regional anesthesia
(7) NMDA-receptor-channel blocker [benzodiazepine? α-agonist? IV lidocaine?]
(6) Lidocain patch (if localized pain)
(5) Tricyclic Antidepressant and Ca-channel α2-δ ligand
(4) Tricyclic Antidepressant (or Ca-channel α2-δ ligand) ± ketamine
(3) Opioid (plus non-opioid) analgesics [consider Tramadol or Methadone]
(2) Integrative therapies; manage comorbidities (anxiety, sleep disturbances)
(1) Identify and treat underlying disease process (radiation?) (corticosteroids?)

Conclusions

- 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: Opioids (?), Amitriptyline, Gabapentin
- Low-dose Ketamine may represent a potent adjuvant analgesia

Further Training

8th Annual Pediatric Pain Master Class | Minneapolis, MN | June 20-26, 2015
Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer | Chicago, IL, Oct 16-17, 2014
Center to Advance Palliative Care (CAPC) - Pediatric Palliative Care Leadership Center (PCLC) Training | Dec 10-12, 2014