Advanced Pain Prevention and Treatment in children with progressive neurologic, metabolic or chromosomally based condition with impairment of the CNS

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
stefan.friedrichsdorf@childrensMN.org

Objectives

- Appreciate high prevalence of complex and neuropathic pain in children with Intellectual Disability
- Define complex and neuropathic pain and describe main causes in pediatric patients
- Develop a step-by-step treatment approach for complex and neuropathic pain in this patient group

Pain in children with progressive neurologic, metabolic or chromosomal conditions with impairment of the central nervous system

- Little known about prevalence, characterization and treatment of pain in these children
- Pain common, under-recognized and undertreated
- 53% experiencing pain; older, more comorbidities such as dyspnea/feeding difficulties, less mobile with lower functional skills
- 41% percent of children with parent-reported pain (21.8% of all patients) experienced pain most of the time
- Majority of clinicians (60%) not documenting pain assessment or analgesic treatment in medical records of patients who were experiencing pain
- Documentation of pain in the medical record positively correlated with children receiving palliative care services and being prescribed analgesics, such as acetaminophen, NSAIDS, opioids, gabapentin and amitriptyline.
**Prevalence 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</th>
<th># of placebo controlled studies</th>
<th># of participants</th>
<th>Pain Relief</th>
<th>Placebo NNT</th>
<th>NNNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox A (4)</td>
<td>137</td>
<td>60%</td>
<td>6%</td>
<td>1.9</td>
<td>ns</td>
</tr>
<tr>
<td>TCAs (15)</td>
<td>948</td>
<td>45.9%</td>
<td>17.9%</td>
<td>3.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Strong Opioids (7)</td>
<td>838</td>
<td>51.9%</td>
<td>26.2%</td>
<td>4.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Tramadol (6)</td>
<td>741</td>
<td>46.3%</td>
<td>26.6%</td>
<td>4.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Gabapentin (14)</td>
<td>3503</td>
<td>34.7%</td>
<td>20.3%</td>
<td>6.3*</td>
<td>25.6</td>
</tr>
<tr>
<td>Serotonin-noradrenaline reuptake inhibitor (10)</td>
<td>2541</td>
<td>43.4%</td>
<td>28.3%</td>
<td>6.4</td>
<td>11.8</td>
</tr>
<tr>
<td>Pregabalin (25)</td>
<td>5940</td>
<td>38.5%</td>
<td>24%</td>
<td>7.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Capsaicin 8% (6)</td>
<td>2073</td>
<td>35.9%</td>
<td>27.4%</td>
<td>16.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

* extended release gabapentin NNT: 8; NNH 21.9 ns=non significant

Advanced management of pain in PPC: Step 4

(1) Identify and treat underlying disease process (radiation?) (corticosteroids)
(2) Integrative therapies & Rehabilitation manage comorbidities (anxiety, sleep disturbances). Psychological Therapies.
(3) Basic Analgesia plus Opioid
(4) 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

---

**Multimodal (Opioid-sparing) Analgesia**

- **Basic Analgesics**
  - 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 opioid
  - Neurolysis - normal anatomy

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

- **Psychology**
  - CBT

- **Rehabilitation**
  - Exercise, Physical Therapy
  - Sleep Hygiene
  - OT

- **Adjuvants**
  - Alpha-Agonists
  - Gabapentinoids
  - TCA/Antidepressants
  - NMDA-Antagonists
  - Na-channel blockers
  - Antispasmodics
  - Benzodiazepines
  - Corticosteroids
  - Muscle relaxants
  - Radiotherapeutics
  - Bisphosphonates

- **Spirituality**

---

**Adjuvant Analgesia**

Small Group work, please
Advanced management of pain in PPC: Step 5

- Dose Amitriptyline?
  - 20 kg x 0.1 -> 0.4 mg/kg = 2 mg -> 8 mg QHS (once at night)

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

Tricyclic antidepressants

- Amitriptyline (or Nortriptyline)
- Dose (for both): 0.1 mg/kg PO QHS, slowly increase to max 0.4-0.5 mg/kg (max 5-10 mg, escalate to 20-25 mg)
- (adult) NNT: 3.6
- Side effects: sedation, anticholinergic effects, prolonged QTc
- Wean over 1 week

Other antidepressants

- Cannot be recommended
- Much less evidence for use
- SSRIs – NNT 6.8
- SNRI – NNT 6.4
  - Not shown as effective antidepressant as SSRIs in pediatric patients
- Neonates: Gabapentin first line, TCAs second line
Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Thalamus

Periaqueductal grey (endorphins)

Integrative (non-pharmacological) therapies

TCA
SSRIs
Methadone
Tramadol

Acetaminophen (Paracetamol)

NSAIDs

Tricyclic Antidepressants:
(+) Opioid analgesia via serotoninergic mechanism at brainstem

Advanced management of pain in PPC: Step 6

• Dose gabapentin?
• 6 -> 24 mg/kg TID x 20 kg = 120 mg -> 480 mg TID (three times per day)

(6) Tricyclic Antidepressant and gabapentin

(5) Tricyclic Antidepressant (or gabapentin) ± low-dose ketamine

(4) Regional anesthesia, if appropriate

(3) Opioid analgesics plus NSAID

(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)

G

Presynaptic nerve terminal

Postsynaptic nerve terminal

↓ Glutamate ↓ Substance P
Gabapentoids

- Mechanism: calcium-channel blocker, decrease release of pain transmitters
- Gabapentin
  - Dosage: 2-6 mg/kg/dose start QHS, then BID then TID then escalate over 2-8 weeks to max 24 mg/kg/dose (adult 100-300 start, escalate to 600-1,200 mg TID)
  - Infants: 4 ->18 mg/kg/dose Q6h
  - (adult) NNT: 6.3
  - Side effects: nystagmus, thought disorder, hallucinations, headache, myalgia
  - Wean over 1-2 weeks
- Other option: pregabalin - off-label
  - Dosage: 1/6 of gabapentin dose BID

TCA & gabapentoid

- Efficacy of TCAs and gabapentinoids equal
- Mechanism completely different
- Combination recommended, if single adjuvant ineffective
- Neonates 0-6 months
  - gabapentin first choice Q6h (!)
  - low-dose amitriptyline added, if ineffective

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

- Thalamus
- Periaqueductal grey (endorphins)
- Integrative (non-pharmacological) therapies

- TCA, SSRI, Methadone, Transdermal

- Combination: Amitriptyline & Gabapentin

- Inhibitors of excitatory glutamate systems: Gabapentin/Pregabalin, Carbamazepine
- Valproate

- Acetaminophen (Paracetamol)
- Opioids
- NSAIDs
Advanced management of pain in PPC: Step 7

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Opioid analgesics plus NSAID / APAP
4. Regional anesthesia, if appropriate
5. Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
6. Tricyclic Antidepressant and gabapentinoid
7. Lidocain; (patch, if localized pain).

Other Sodium Channel Blocker

- **IV Lidocaine** for cancer pain: n=51 adult patients: without ECG monitoring: 5 mg/kg infused over 1 hour, option for subsequent doses increased if necessary, maximum of 10 mg/kg; effective analgesia in 49%

- **Subcutaneous lidocaine** infusions may be used safely in cancer pain management and is effective in some patients

- **Oral mexiletine, tocainide, flecainide**: High side effect liability from oral drugs

- **How about local lidocaine and novocaine...?**

Advanced management of pain in PPC: Step 8

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Opioid analgesics plus NSAID / APAP
4. Regional anesthesia, if appropriate
5. Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
6. Tricyclic Antidepressant and gabapentinoid
7. Lidocain; (patch, if localized pain).

*HOT OFF THE PRESS*
NMDA-receptor-channel blockers:
Ketamine

- Dissociative anesthetic, analgesic at low doses
- Low-Dosage:
  - IV – 1 mcg/kg/min, escalate to 5-10 mcg/kg/min
    (adult: 3 mg/hr escalate to max. 15-30 mg/hr)
  - PO – 0.2-0.4 mg/kg TID-QID and PRN (adult 10-25 mg,
    escalate to max 50 mg QID)
- Side effects (usually not at low-dose): intracranial hypertension, tachycardia,
  psychomimetic phenomena – consider benzodiazepine

Other adjuvants . . .

- **Alpha-agonists**
  - Clonidine, Dexmedetomidine
- Benzodiazepines
- SNRI
- Cannabis
  - dronabinol, nabilone
- Botulinum toxin A
- Palliative Chemotherapy
- Propofol

α-Adrenergic Agonists

**Analgesic effect?**

- Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate same K-
  channel via inhibitory G protein-proteins
- Presynaptic alpha-2-adrenoreceptors 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: Dexmedetomidine vs Clonidine**

- **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).

**Clonidine**

- **PO:** 1-3 mcg/kg Q4-6h
- **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
   - Adult NNSN Weaning Document: starting dose 1 mcg/kg/hr (up to 4 mcg/kg/hr)

**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
  - Withdrawal effects were noted in patients following prolonged infusion.
Dexmedetomidine in Neonates

- Pharmacokinetics, safety, and efficacy 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. Pediatr Pharmacol Ther, 17(3): 252-262.


- 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

Benzodiazepines

(incl. diazepam, lorazepam, midazolam, clonazepam)

- 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.
**SNRI**

- NNT: 6.4; NNH: 11.8


- Duloxetine, venlafaxine

---

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

Injury

- Thalamus
- Integrative (non-pharmacological) therapies
- TCA
- SIBs
- Methadone
- Transmolar

Stimulation of inhibiting GABA system
- Sedatives
- Benzodiazepines
- Valproate

**Inhibitors of excitatory glutamate systems:**
- Gabapentin/Pregabalin
- Carbamazepine
- Valproate

**Carbamazepine* 2nd Neuron**
- Periaqueductal grey (endorphins)
- Integrative (non-pharmacological) therapies

**Acetaminophen (Paracetamol)**

**Opioids**
- NMDA-Channel Blockers
- Ketamine
- Methadone
- Stimulation of inhibiting GABA system
- Baclofen
- Benzodiazepines
- Valproate

**Sodium-channel blockade**
- Carbamazepine*
- Lidocaine

**Cannabinoid Adult RCT**

- Cannabinoids: NNT: ns; NNH 12.1
- Only 2 out of 9 trials positive


- Cannabinoids as adjunctive analgesia in advanced cancer patients with uncontrolled pain?

- RCT (n=397): nabiximols (Sativex®), extract of Cannabis sativa 2 cannabinoids (Δ9-tetrahydrocannabinol [27 mg/mL] and cannabidiol [25 mg/mL]), in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy
  - not superior to placebo on the primary efficacy endpoint

---

* PRESS *
Early-Onset, Regular Cannabis Use Is Linked to IQ Decline


Cannabis

- Correlation with mental illness

- Health issues associated with cannabis
  - Lowers sperm count
  - Gynecomastia in boys
  - 3 studies show positive correlation between marijuana use and testicular cancer

- Impairment of driving ability
- Associated with drugs of abuse
- Impacts on work

Positive Effects

Cannabinoids

- May result in reduction of pain and inflammation
- Work as an antiepileptic in some children
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)

Pain profiles of Adolescent and Young Adult Recreational Marijuana users

- AYA recreational marijuana users frequently use marijuana to relieve pain “most of the time,” despite that it is NOT an effective analgesic for them.

<table>
<thead>
<tr>
<th>Pain Characteristics</th>
<th>M (SD) Pain Intensity</th>
<th>F(1,133)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual pain intensity</td>
<td>3.49***</td>
<td>150.48***</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Headache/migraine</td>
<td>5.08**</td>
<td>11.35***</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Joint pain</td>
<td>4.48**</td>
<td>9.16**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.76*</td>
<td>2.86*</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Note:** *P*/**P*/***P*/****P* indicates statistical significance at .05/.01/.005/.001 levels, respectively.

**Results**

At present, little is known about the pain profiles of AYA recreational marijuana users.

Chronic pain was common in this sample of AYA marijuana users; despite being a community sample, their pain characteristics were similar to those observed in treatment settings.

Despite frequent use to relieve pain, many users continue to experience significant and persistent pain and pain-related quality of life in users with and without chronic pain.

Nearly half of the community sample (45.8%) reported a current weekly pain problem of > 3 months duration.

Approximately half those reporting chronic pain also endorsed clinically significant pain (PHQ > 10). Over half (54.5%) also endorsed clinically significant pain (PHQ > 10).

Usual pain intensity was in the moderate to high range (M = 3.49***).

Primary pain locations were musculoskeletal (57.6%), headache/migraine (19.7%), joint (12.1%), and abdominal (9.1%).

The majority (66.7%) reported pain in multiple locations.

The overarching objective of this study was to examine the pain characteristics of AYA recreational marijuana users, and to compare health consumption patterns and health behaviors.

**Pain Characteristics**

**Pain Intensity:** Usual pain intensity was in the moderate to high range (M = 3.49***).

**Pain Location:**

- Musculoskeletal: 57.6%
- Headache/migraine: 19.7%
- Joint: 12.1%
- Abdominal: 9.1%

**Pain Frequency:**

- Daily or multiple times daily: 63% (M = 2.86; 43.8%)
- 1-2 times per week: 29% (M = 2.49; 29.8%)
- 1-2 times per month: 9% (M = 2.00; 9.2%)
- Once per month or less: 9% (M = 1.68; 9.2%)

**Marijuana Consumption Patterns:**

- Current weekly use: 29% (M = 2.23; 29.8%)
- Using marijuana at least once a week: 46.99 (21.73)
- Using marijuana once a week or less: 24.1% (M = 2.00; 9.2%)

**Marijuana Effects:**

- Relaxation: 88.24 (29.76)
- Increased appetite: 71.32 (18.41)
- Altered mood: 63.90 (17.73)

**Marijuana Motives:**

- AYA recreational marijuana users frequently use marijuana to relieve pain “most of the time,” despite that it is NOT an effective analgesic for them.

**Analytic Procedure**

- **Univariate Analyses:** The pain and health-related quality of life subscales were compared between groups using **ANOVA**.
- **Supplemental Analyses:** For assessing the cumulative burden of pain, **PROMIS** pain interference scales were compared between groups using **MANOVA**.

- **Results:** Users with chronic pain reported worse physical and social functioning, bodily pain, general health, social functioning, energy/fatigue, and role limitations due to physical health. Users with chronic pain also reported elevated disability scores compared to those without chronic pain.

**Conclusions:** Despite frequent use to relieve pain, many users continue to experience significant and persistent pain and pain-related quality of life. Chronic pain was common in this sample of AYA recreational marijuana users; despite being a community sample, their pain characteristics were similar to those observed in treatment settings.
Low-dose Propofol

- 3-year old: 1.2-36 mg/kg/h Glover

- 13 adults (mean): Nausea 0.6 - 1 mg/kg/h, Sedation: 0.9-2.1 mg/kg/h Lundstrom S, Zachrisson U, Furst CJ. When nothing helps: propofol as sedative and antiemetic in palliative cancer care. J Pain Symptom Managem, 30(6):570-7, 2005


- Titration (Anesthesia!): IV infusion - in increments of 10 mcg/kg/min?

So, how do we treat the individual pain patient in front of us?

Crystal clear answer:

"It Depends"
-Socrates
Advanced management of pain in PPC: Step 9

(9) Palliative Sedation?
(7) Lidocaine; (patch, if localized pain).
(6) Tricyclic Antidepressant and gabapentinoid
(5) Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
(4) Regional anesthesia, if appropriate
(3) Opioid analgesics plus NSAID / APAP
(2) Integrative therapies & Rehabilitation: manage comorbidities (anxiety, sleep disturbances), Psychological Therapies.
(1) Identify and treat underlying disease process (radiation?) (corticosteroids?)

Further Training
Contact: CIPPC@ChildrensMN.org
SAVE THE DATE:
• Education in Palliative & End-of-Life Care (EPEC) Pediatrics: Become an EPEC-Pediatrics Trainer Conference, Oct 3-4, 2019 plus optional EPEC-Pediatrics Professional Development Workshop; Oct 5, 2019
• 12th Pediatric Pain Master Class in Minneapolis, MN, June 13-19, 2020