The Management of Neuropathic Pain and Use of Adjuvant Analgesia in Children

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- Appreciate high prevalence of neuropathic pain children with serious illnesses ["Attitude"]
- Define neuropathic pain and describe main causes in pediatric patients ["knowledge"]
- Develop a step-by-step treatment approach for neuropathic pain ["skill"]
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)

Sarah’s Pain score is documented as 5/10

- 12-year girl, 3-year history of Ewing Sarcoma, poor response to cancer-directed chemotherapy, surgery, radiation
- Metastases in lung, liver; large primary tumor in left hip infiltrating spinal cord and compressing left sciatic nerve
- You would like to know more about potential neuropathic pain. What might you hear from your colleagues why this information is not documented nor available for last 12 months?

Prevalence

- Prevalence of neuropathic pain in children unclear
- Probably not in infants…?
  - Brachial plexus injury in newborns
  - Rats not before P7 to P21, i.e. 4-5 months in children...
  - Damage early on: no memory…adaptive immune system…?
Is it Neuropathic Pain...

- Children with CP: Daily pain 8.1%  

- Cognitively impaired, non-communicating children: Daily pain 23.5%  

- 275 children with progressive, non-curable genetic, metabolic, or neurological conditions: Pain 53% [Most of the time: 21.8%]  

- Some genetic factors underlying development of neuropathic pain and chronic widespread pain are the same  

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

- Phantom limb pain: 60 - 80% of adult patients with amputation experience phantom sensations in their amputated limb, majority are painful  

- Autoimmune and degenerative neuropathies: Guillain-Barré syndrome; Charcot-Marie-Tooth disease  

Potential Causes Include

- 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
Pain in Children with Mitochondrial Diseases?

- Animal model: Mitochondria play important role in inflammatory and neuropathic pain
- Inhibition of 2 key mitochondrial functions (ATP generation, reactive oxygen species) -> attenuate protein kinase C[epsilon] dependent form of mechanical hyperalgesia
- Dorsal root ganglion: Accumulation of mitochondria (in vitro by nerve growth factor)


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


IASP Definitions 2011

- Paresthesia: An abnormal (not unpleasant) sensation, whether spontaneous or evoked.
- Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.
- After much discussion, it has been agreed to recommend that paresthesia be used to describe an abnormal sensation that is not unpleasant while dysesthesia be used preferentially for an abnormal sensation that is considered to be unpleasant.
- Alloodynia: Pain due to a stimulus that does not normally provoke pain
- Hyperalgesia: Increased pain from a stimulus that normally provokes pain.
Neuropathic Pain Assessment

Evaluate for
- Paroxysmal pain
- Paresthetic or dysesthetic sensation

Use age-appropriate pediatric scales for acute pain instead, including
- VAS (or numerical pain rating scale) 0-10
- Faces scales-revised
- FLACC
- CRIES
- COMFORT

Descriptions might include:
- numbesness
- tingling
- burning
- electric-like
- shooting
- raw skin

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

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
Current Status: Call for Action

- Large number of children with advanced cancer and non-malignant serious conditions experience neuropathic pain
- However, neuropathic pain is not routinely assessed
- Children are often not effectively treated

Pharmacotherapy for neuropathic pain in adults

<table>
<thead>
<tr>
<th>Medication (# of placebo controlled studies)</th>
<th># of participants</th>
<th>Pain Relief</th>
<th>Placebo</th>
<th>NNT</th>
<th>NNH</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>10.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

* extended release gabapentin NNT: 8; NNH: 31.9
ns=non significant

Pediatric Relevance of Adult Evidence?

- Adults usually suffer from conditions such as diabetic neuropathy, trigeminal neuralgia, shingles, HIV neuropathy etc.
- Children usually do not
Case Report 1: 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

Case 2: Alexi “Lexi”

- 14-month-old (10 kg)
- Fanconi’s Anemia
- Multiple long-term hospitalizations for complications of therapy
- Listed for bone marrow transplant
- Recently had a bleed in her brain, and new neurological changes
Case 2: Lexi
[EPEC-Pediatrics]

- Jenny, age 22, single mom, has a history of depression and anxiety & maternal grandmother.
- 1 sibling, Bobby Jr, age 5 yrs
- Jenny presents to the clinic unexpectedly with Alexis, and has sibling with her

Clinical case on trigger video

Exam & history suggest neuropathic pain...

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

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

(2) Integrative therapies & Rehabilitation manage comorbidities (anxiety, sleep disturbances). Psychological Therapies.

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

Interaction between autonomic and somatosensory systems

- Clinically, sympathetically maintained pain may manifest as temperature or color changes (or both) in affected extremity, swelling or atrophy, and pain worsened by cold weather or stress, which enhances sympathetic outflow. Cohen, S.P. and J. Mao. Neuropathic pain mechanisms and their clinical implications. BMJ, 2014. 348: p. f7656

- Sympathetically maintained pain most commonly linked to CRPS, but same principles apply to other pain conditions, such as postherpetic neuralgia. Cohen, S.P., S.G. Kapoor, and J. Rathmell. Intravenous infusion tests have limited utility for selecting long-term drug therapy in patients with chronic pain. J Pain. 2007 Jan; 8(1):50-61.

- Interaction between anatomically distinct autonomic and somatosensory systems is complex but probably includes:
  - expression of α-adrenoceptors on primary afferent sensory fibers
  - sympathetic sprouting into dorsal root ganglia
  - impaired oxygenation and nutrition in response to sympathetically mediated vasoconstriction.

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

Integrative Pain & Symptom Management


Integrative Pain Management

- Behavioral Therapies
  - Breathing
  - Imagery
  - Hypnosis
- Individual Psychotherapy
- Physical Therapy
- TENS
- Exercise
- Stockings
- Make-a-wish

Case Report: Clark
In other words...

- Adult data: Despite best of care and sequential trials of pharmacological therapies: 40-60% of patients remain unrelieved or inadequately relieved. 
- In the treatment of medium to severe neuropathic pain in children medications alone are not sufficient.
- Management likely inefficient without:
  - PT/OT
  - Integrative Therapies
  - Psychological therapies (patient or parents)

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

Interventional management of neuropathic pain in adults

- 4 weak recommendations based on the amount and consistency of evidence, including degree of efficacy and safety, are:
  - (1) Epidural injections for herpes zoster
  - (2) Steroid injections for radiculopathy
  - (3) Spinal cord stimulation (SCS) for failed back surgery syndrome
  - (4) SCS for CRPS type 1 (who do not respond adequately to noninvasive treatments and sympathetic nerve blocks)
- Based on the available data, we recommend not to use sympathetic blocks for PHN nor radiofrequency lesions for radiculopathy
Regional anesthesia approaches to pain management in PC

- 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

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 NSAIDs

NSAIDs for Neuropathic Pain

Diclofenac-Patch

- NSAID
- Analgesic action of topical diclofenac: peripheral NMDA receptor antagonism? Dong XD, Svensson P, Cairns BE. The analgesic action of topical diclofenac may be mediated through peripheral NMDA receptor antagonism. Pain. 2009 Dec 15;147(1-3):36-45.

Opioids for Neuropathic Pain

“Weak” opioids (= multimechanism)
- Tapentadol! Bias; NNT 10.2
- No additional benefit > 180 mg morphine equivalent

Case Report: Clark

- 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
- Methadone PO 10 mg TID -> 12.5 mg TID
Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury → Thalamus

Acetaminophen (Paracetamol)

Opioids

NSAIDs

Injury

Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

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

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

PSYCHOLOGY
- CBT

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

Opioids
- Tramadol (“weak”)
- Morphine (“strong”)

4 WHO-Principles
- “By the clock”

Pain Management

Integrative (non-pharmacological) therapies

Descending pathways that modulate transmission of nociceptive signals originate in periaqueductal gray (PAG), locus coeruleus, anterior cingulate, amygdala, and hypothalamus. These pathways are relayed through brainstem nuclei to spinal cord. Inhibitory transmitters involved in these pathways include norepinephrine, 5-hydroxytryptamine, dopamine, and endogenous opioids.
Management of Neuropathic Pain in Pediatrics  
Suggested “Non-Evidence-based” Step-by-Step Approach

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

(2) Integrative therapies & Rehabilitation: manage comorbidities (anxiety, sleep disturbances). Psychological Therapies.

(3) Regional anesthesia, if appropriate

(4) NEW onset: Opioid analgesics (consider Tramadol or Methadone) plus NSAID

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

Case Report: Clark

(1) TRICYCLIC ANTIDEPRESSANT
  - Amitriptyline 5 mg -> 25 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

Amitriptyline

- NNT: 3.6; NNH: 13.4 
- No dose-response effect
- Nortriptyline: only 1 study

- Efficacy of TCA in central pain

- n=39; superior efficacy of a nortriptyline-morphine combination over either monotherapy (plus gabapentinoid?)

- 2 studies (high effect size): no effect of amitriptyline in HIV neuropathy
Tricyclic antidepressants (TCA)

- Relieve various neuropathic pain
  2 studies: no effect of amitriptyline & nortriptyline in chemotherapy-induced neuropathy (pain not primary outcome)
- 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

- Tricyclic Antidepressants:
  (+) Opioid analgesia via serotonergic mechanism at brainstem
- Integrative (non-pharmacological) therapies
- NSAIDs
- Opioids
- Acetaminophen (Paracetamol)
- Periaqueductal grey (endorphins)
- Thalamus
- Injury
- TCA
- SSRI
- Methadone
- Tramadol
Management of Neuropathic Pain in Pediatrics
Suggested “Non-Evidence-based” Step-by-Step Approach

(6) Tricyclic Antidepressant and gabapentinoid
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Gabapentinoids: Ca-channel α2-δ ligands

Voltage-gated Ca-channel
Presynaptic nerve terminal
↓ Glutamate
↓ Substance P
Postsynaptic nerve terminal
α2-δ subunit [dysfunction/upregulation role in neuropathic pain]
Gabapentinoids: Ca-channel α2-δ ligands

There are 4 subtypes of the α2-δ ligands, gabapentinoids bind to subtype 1 and 2 only. This modulation causes:

- After nerve injury, expression of α2δ calcium channels increases in and around dorsal root ganglia, increasing excitability.


- Gabapentin (Neurontin) 300 mg TID
- Gabapentin (Neurontin) 900 mg / day
- Gabapentin 900 mg / day
- Pregabalin 150 mg / day
- Pregabalin 150 mg / day
- Pregabalin 75 mg BID

Gabapentin: Ca-channel α2-δ ligands

- Conversion from Gabapentin (Neurontin)
  to Pregabalin (Lyrica)
- Approximately 6-7:1

Gabapentin: NNT: 6.3; NNH: 25.6


- 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
**Pregabaline**

- Efficacy worse than gabapentin
- Dose-response (600mg/day more effective than 300 mg/day)
- Linear (pregabalin) versus non-linear (gabapentin) bioavailability: Clinical relevance unclear.
- Adverse effects include: Weight increase, dizziness, somnolence, blurred vision, life-threatening angioedema (face, mouth, larynx) - careful concurrent administration with ACE inhibitors

**Pediatric data**


<table>
<thead>
<tr>
<th>Age range</th>
<th>Less than 6 months or 1 year</th>
<th>11 – 27 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average daily dose</td>
<td>50 mg/ kg/day (25-75 mg/kg/day)</td>
<td>35 mg/ kg/day (25-45 mg/kg/day)</td>
</tr>
</tbody>
</table>

Suggested guidelines:
- Start at 2-4 mg/kg/day
- Increase up to 5-10 mg/kg/day in those < 6 years

**Gabapentin**

- 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]
- Example: 10-year-old girl, 30 kg
  - 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
- Adverse effects include: ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, (peripheral edema)
- wean: decrease gradually x 1-2 weeks!
- Effect: days - weeks
Gabapentin for Acute Pain?

- Postop: 13-32 mg morphine reduction

- Total knee replacement: Decreased post-op opioid use, improved functional recovery

- Gabapentin may have a limited if any role in acute postoperative pain management of opioid-naive patients undergoing total knee arthroplasty

- Hip arthroplasty: did not result in better analgesia, less opioid use, nor improved functional recovery

- Laparoscopic cholecystectomy: combination with meloxicam did not result in enhanced pain relief

Gabapentin postoperatively?

- 17-day, term infant, 3kg, TGA (post OP day #15), day 10 post ECMO; max. fentanyl 8 mcg/hr, episodes of severe irritability (pain? withdrawal?) unrelieved by opioids, dexmedetomidine:
  - 04/10/2012: Gabapentin 4 mg/kg Q6h

Gabapentinoids & TCAs?

- Non-placebo controlled study: Nortriptyline & gabapentin (at maximum tolerated doses) provided greater analgesia (plus improved sleep & mood) than when each drug was administered alone

- Comparative Drug Trials

- Metaanalysis: 6 RCTs - TCA vs gabapentin/
Pregabalin: No difference
Other Antiepileptic Drugs


- Poorest safety profile:
  - Topiramate NNT 6; NNH 6.3
  - Zonisamide NNH 2.0

- Oxcarbazepine / carbamazepine NNH 5.5

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(4) LIDOCAINE
  - 5% patches Q12h on/off
Glucocorticosteroids

- Possibly helpful:
  - Nerve root / nerve trunk compression (e.g. tumor infiltration brachial plexus / lumbosacral plexus)
  - Spinal cord compression
  - Bone metastasis
  - Bowel obstruction
  - Lymphedema

- Effect:
  - Antiedematous (ameliorate painful nerve or spinal cord compression)
  - Antiinflammatory
  - Directly lyse some tumors (e.g. lymphoma)

- Adverse effects: Mood swings, Cushing's syndrome, pituitary-adrenal axis suppression, peptic ulcer, immunosuppression
  - Psychosis - consider steroid switching
  - Concurrent administration with NSAIDs: Risk of life-threatening GI bleeding x 5-fold
  - Use gastroprotective agent (!)

Dosage iv/po: Dexamethason (glucocorticoid): 0.1 - 1.5 mg/kg (max. 10mg) starting dose, then 0.1 - 0.25 mg/kg x2/day (for < 14 days)

Malignant spinal cord compression (adult dose): Dexamethason 16-96 mg/day or equivalent

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7. Lidocain patch (if localized pain).
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Sodium channels are involved in pain...


Topical Lidocaine


- Cochrane analysis: Small, short-term trials indicate topical lidocaine may be effective in treating neuropathic pain; safety & tolerability were good in all cases Cherry S, Wiffen P, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev 2014;7:CD010958.

Topical Lidocaine 5% patch

- RCT (n=87) effective adjunct in post-operative (knee replacement) pain management. Nafissi A: Lidoderm’s effectiveness in reducing pain in post-operative unilateral knee replacements patients. 30th Annual Scientific Meeting of the American Pain Society May 2011 (Poster)
- 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?]

IV Lidocaine - Pediatric Experience

- Nausea after 4 days? Neuropathic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mcg/mL
  - Case report; end-of-life cancer care:

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%
- Oral mexiletine, tocainide, flecainide: High side effect liability from oral drugs: Not recommended
- How about local lidocaine and novocaine...?
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Opioid induced tolerance and hyperalgesia

Rats: Oxycodone and Ultra-low-dose naloxone

Chronic administration: Shift
Opioid induced tolerance and hyperalgesia

- Opioid
  - mu-receptor

- G proteins
  - stimulation

- Protein Kinase-
  - C
  - activation

- Other neuromodulators

- Inhibition of Ca
  - channels
  - neurotransmitter
  - release

- Alter response characteristics of neuron => hyperpolarization

- 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
NMDA-Receptor Channel Blocker

2. Membrane potential changed as a result of excitation
   - Opioid-sensitivity
     - Central (dorsal horn) sensitization
     - radiation of pain
     - spontaneous pain
     - Hyperalgesia, allodynia

Magnesium as Analgesic?

- 2007: systematic review, no analgesic evidence (postoperative, adjuvant)


- 13 RCTs, all but 2 reported reduced postop pain & analgesic requirements
- 8 RCTs spinal Mg: lower pain scores & analgesic requirements
- Administration: IV (severe hypo-Mg), PO (mild)

Central Sensitization

Central Sensitization


NMDA-Receptor Channel Blocker

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

NMDA-Receptor Channel Blocker

- Central NMDA receptors
- NMDA receptors in supraspinal facilitatory sites (such as rostral ventromedial medulla, nucleus gigantocellularis) maintain non-inflammatory muscle pain in animal model Da Silva LF, Desantana JM, Sluka KA. Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. J Pain. 2010 Apr;11(4):378-87.
- No ketamine evidence
Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture [S(+)]-enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]
- 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]
  PO: 0.2-0.5 mg/kg TID-QID
  and PRN (sc, sl, intranasal, pr, spinally)
- Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose!!

Low-dose Ketamine

- Action which may contribute to analgesic effect: Meller S, Pain 1996. 68:435-6
  - Cholinergic transmission
  - Noradrenergic / serotonergic re-uptake inhibition
  - μ, δ, κ - opioid-like effect
  - Interactions with other Na-/Ca- channels

Low-dose Ketamine - Adult Evidence

- 37 RCTs (n=2240): subanesthetic Ketamine effective in reducing morphine requirements in first 24 hours after surgery; reduces postoperative nausea and vomiting; Adverse effects are mild or absent. Bell RF, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006 Jan 25;(1):CD004603


Low-dose Ketamine - Pediatric Evidence

- no RCT’s, few case reports
- Finkel JC, J Pain 2007; 8(6):515-21
- n = 11, terminal cancer, age 3-17
- Starting dose: 0.1-0.2 mg/kg/hr (max 1 mg/kg/hr)
- Lorazepam 0.025 mg/kg BID
- n = 8/11: ↓ Pain; ↓ Opioid requirements (28-100%)
- No psychotropic side effects, no hallucinations


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
- Estimated at 1:1-1:3 (i.e. 1 mg IV = 1-3 mg PO)
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

3 unsuccessful trials of decreasing/discontinuing dose
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]

• Hypertonic at baseline, initially MAP increase by 10-15 mm/Hg
• Absent benzodiazepine -> no psychotropic adverse effects

Case Report: Clark

Low-Dose Ketamine:
Case Example

Case 2: 17-year-old
Hydromorphone PCA
Start: Ketamine

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:** 25 mg QHS

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

**Lidocaine Patches:** Discontinued after 3 weeks

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**Benzodiazepines** (incl. diazepam, lorazepam, midazolam)

- **Mechanisms of action:** gamma-aminobutyric acid (GABA) receptors

  - Potentiation of GABA-mediated transmission: sedative, anxiolytic, and anticonvulsant actions

  - GABA-agonist activity in the limbic cortex: amnestic property


  - 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

α-Adrenergic Agonists

Analgesic effect?

- Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory Gαi0-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: Clonidine vs Dexmedetomidine

- **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). Dexmedetomidine increased the risk of postoperative bradycardia (NNH 3).

**Clonidine**

- **PO**: 1-3 mcg/kg Q6h
- 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 [Athens, Greece 5/16/2014]
  - Adult NHS Wolverhampton Guidelines starting dose 1 mcg/kg/hr [up to 4 mcg/kg/hr]
- **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

**Dexmedetomidine**

- **Used in palliative care**
- **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
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 of dexmedetomidine 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.
- 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).

Cannabis

- > 60 active compounds extracted from cannabis
- Activation of endocannabinoid system suppresses behavioral responses to acute and persistent noxious stimulation
  - Central and peripheral mechanisms
  - Cannabinoid receptors: periaqueductal gray (PAG), rostral ventro-medial medulla, dorsal horn of spinal cord
  - Animal experiments: Cannabinoids produce analgesia and potentiate opioids, particularly in neuropathic pain

Medical Cannabis program currently (2014) in 22 US states plus Washington, D.C.

State adult population registered for medical marijuana:

- Montana: 4.1%
- Vermont: 0.07%

Cannabis

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

- Nabiximol (Sativex) oromucosal pump spray: D-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in 1:1 ratio

  Effective for MS patients with neuropathic pain

RCT Cancer pain: not effective

- Correlation with mental illness


- Impairment of driving ability

- 3 studies show positive correlation between marijuana use and testicular cancer


- Impairment of driving ability

- Associated with drugs of abuse

Cannabis

- RCT Cancer pain: not effective
Early-Onset, Regular Cannabis Use Is Linked to IQ Decline


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 grown up to 10,000,000/gram organisms Salmonella muenchen (incl. 85 cases of acquired enteritis in Georgia, Alabama, Ohio, Michigan)
**Cannabis**
San Diego, CA

- AAP Handout for parents "Despite relaxed regulations, marijuana harms developing brain":
  [AAP Handout](http://aapnews.aappublications.org/content/36/3/4.full.pdf+html)
- Updated AAP policy opposes marijuana use, citing potential harms, lack of research
  [Updated AAP Policy](http://aapnews.aappublications.org/content/early/2015/01/26/aapnews.20150126-1)

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**Capsaicin**

- Sensory-Selective (Nociceptive-Selective) Nerve Blockade: Schumacher MA, Eilers HE.

  - TRPV1 channels are located in small sensory fibers, not large fibers
  - Capsaicin, the substance that makes chili peppers hot, opens TRPV1 ion channels in small sensory fibers
  - Open TRPV1 channels permit entry of the quaternized lidocaine analogue QX-314

- 5 of 7 studies for post-herpetic neuralgia (30 min) or HIV-related painful polyneuropathy (60 min): single application effective NNT: 10.6; NNH: ?
Capsaicin

- Either as repeated application of a low dose 0.025%, 0.075%, 0.1% cream x3-4/day, length empirical, or a single application of a high dose (8%) patch
- FDA approved 2010: 8% capsaicin patch (Quenzena®) for postherpetic neuralgia (2012 $800 plus MD)
- Administration (with gloves!): 60-minute application, up to 4 patches, once every 3 months
- Adverse effects: application-site redness, pain, itching, papules, increased blood-pressure

Other Adjuvant Analgesic / Co-analgesics

- **Muscle relaxants:** Baclofen; Cyclobenzaprine (Flexan®)
- **Antispasmodics:** Hyoscine butyl bromide (Buscopan®) [not in USA], oxybutynin (Ditropan®), glycopyrrolate (Robinil®)
- **β-ray emitting osteotrope radio pharmaceutical:** e.g. Samarium-153-EDTMP
- **Anti-TNF α agent** [treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpAs)] 
  - Adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi), 

Botulinum toxin A

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

Summary of GRADE Recommendation
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: Amitriptyline, Gabapentin, (Opioids ?)

- Apply WHO principles for acute pain
- Low-dose Ketamine may represent a potent adjuvant analgesia
- Possible Indications: Neuropathic & Nociceptive Pain
- May reverse Opioid-induced hyperalgesia & Opioid tolerance: ↑ opioid efficacy ⇒ ↓ opioid adverse effects

Further Training: CIPPC@ChildrensMN.org

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)