Management of Refractory Pain: Practical Issues and Challenges

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  Twitter: @NoNeedlessPain

Learning Objectives

• Review the causes of and pathophysiologic processes associated with refractory pain in children with blood disorders and cancer
• Discuss strategies for evaluating children with pain refractory to standard treatment
• Better understand available treatment strategies for refractory pain, including integrative (“non-pharmacologic”) approaches, use of newer pharmacologic agents and incorporation of daily opioids

Editorial note: Children with chronic pain are not only suffering physically but also emotionally. It is crucial to address the psychological impact of chronic pain on children and their families. It is important to provide support and interventions that can help children cope with their pain and improve their overall quality of life.

Pediatric Cancer Survivors

• Prevalence of pain during treatment: Outpatient 9-26%, inpatient 39-54%
• Pain frequently reported among survivors of pediatric solid tumors
• Prevalence of pain 12% (pain/abnormal sensation; 15.5% migraines; 20.5% other headaches) and using prescription analgesics higher among survivors than siblings

• Pediatric brain tumor survivors experience many symptoms after treatment. Lack of energy (52%), difficulty with sleep (38%), lack of concentration (36%), and headaches (36%).

• Limited longitudinal and cross-sectional data suggest that Sickle Cell Pain is treatable.

Chronic-on-acute pain

• Treatment of persistent/chronic pain has also largely relied on opioids
• Underlying mechanism poorly understood
• Few studies examining role of peripheral and/or central sensitization
• Opioid-induced hyperalgesia seems likely in some cases but lacks definitive studies

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Refractory Pain

• Pain related to conditions such as cancer or SCD or its treatment, remaining beyond expected time of healing, that has not responded to standard treatment with opioids and co-analgesics
• Usually “Refractory” = “Really Difficult”
• Very rarely “Refractory” = “Refractory” (  
• palliative sedation?)

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

Visceral (internal organs)

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Neurobiology of Sickle-Cell Pain

- Sickle cell pain goes beyond mechanical vaso-occlusion as sole explanation for pain
- Neuroplasticity
- Peripheral/central nervous system sensitization
- Chronic inflammation
- Research suggests that sickle cell disease (SCD) pain has neuropathic component whereas in past pain has been thought to be only nociceptive
- Data support existence of nervous system abnormalities that could contribute to sickle cell pain
- Murine model and humans reveals congruent findings of both heat and cold hypersensitivity in SCD supporting potential abnormalities in the central and/or peripheral nervous system that could explain neurobiology of SCD pain

Chronic Sickle Cell Pain

- Does chronic SCD pain state only result from patients with nociceptive or inflammatory (vasculopathic) pain, recurrent nearly every day?
- Ischemic vaso-occlusive pain not opioid-responsive?
- Model of “Chronic post surgical pain” transition from acute to chronic pain applies?

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

How Do We Manage Acute Pain in Children?

- Non-Opioids: Acetaminophen / Paracetamol
- NSAIDs

Multimodal (Opioid-sparing) Analgesia

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

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Thalamus
- Acetaminophen (Paracetamol)
- NSAIDs
WHO Principle 1: Dosing at Regular Intervals

- **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


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

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.
- Cognitive behavioral techniques (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback)
- Acupuncture, acupressure, aromatherapy
- Physical methods (e.g. cuddle/hug, massage, comfort positioning, heat, cold, TENS)

Integrative Pain & Symptom Management

A Pediatrician’s Top 10 Apps for Distraction & Pain Management: [http://NoNeedlessPain.org](http://NoNeedlessPain.org)
Nociceptive Pathways & Primary Sites of Action of Analgesics

**Injury**

- Opioids
- Acetaminophen (Paracetamol)
- NSAIDs

**Thalamus**

**Periaqueductal grey (endorphins)**

**Integrative (non-pharmacological) therapies**

- Non-Opioids
  - Acetaminophen / Paracetamol
  - NSAIDs

**Opioids**

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

**WHO-Principles**

- “By the clock”

**Integrative Therapies**

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

**Psychology**

- CBT

**Rehabilitation**

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

**Adjuvants**

- Antidepressants
- Anticonvulsants
- Muscle relaxants
- Benzodiazepines
- Corticosteroids
- Bisphosphonates

**Invasive Approaches**

- Regional anesthesia
- Spinal anesthesia
- Epidural or intrathecal
- Neurolytic blocks

**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

**Neuropathic Pain**

- Population prevalence of pain with neuropathic characteristics is likely 6.9% - 10%
- Prevalence of neuropathic pain in children unclear
- Cancer pain > 12 years: Metaanalysis (n=22):
  - Conservative 19%; liberal estimate: 39%

**Potential Causes Include**

- 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
- Cancer-directed chemotherapy, including
  - Vincristine: 50% painful peripheral neuropathy, muscle camps, numbness, tingling (hand, feet)
- Cisplatin: Paresthesias in extremities
- Spinal cord injury: “pain arising as a direct consequence of affecting the somatosensory
Pharmacotherapy for neuropathic pain in adults

<table>
<thead>
<tr>
<th>Medication (if placebo controlled studies)</th>
<th># of participants</th>
<th>Pain Relief</th>
<th>Placbo</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottox 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>4.2</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 (16)</td>
<td>3503</td>
<td>24.7%</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 (23)</td>
<td>5940</td>
<td>38.3%</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

Management of Neuropathic Pain in Pediatrics

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

1. Identify and treat underlying disease process (e.g., radiation?) (corticosteroids?)

2. NEW (!) onset:
   - Opioid analgesics [consider Tramadol or Methadone] plus NSAID

3. Tricyclic Antidepressant or gabapentinoid ± low-dose ketamine

4. Tricyclic Antidepressant and gabapentinoid

5. Lidocain patch (if localized pain)

6. NMDA-receptor-channel blocker [e.g., agonists IV lidocaine! Botox A! benzodiazepines? SNRIs? Capsaicin?]

7. Regional anesthesia, if appropriate

8. Integrative therapies & Rehabilitation: manage comorbidities (anxiety, sleep disturbances)


10. Identifcy and treat underlying disease process (radiation?) (corticosteroids?)

Case Report: Clark at Home

Methadone: 10 mg PO Q8h

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

Pregabalin: 300 mg BID

Amitriptyline: 25 mg QHS

Ketamine: (1-5 mcg/kg/min IV) 40 mg PO PRN Q1h (discontinued after 2 weeks)

Lidocaine Patches: Discontinued after 3 weeks

Pain versus Disability

- Chronic pain is a significant problem in the pediatric population, conservatively estimated to affect 15% to 20% of children.
- Chronic Pain: 15-25% of children, approximately 3% in need of intensive pain rehabilitation
- However, majority of children reporting chronic pain are not greatly disabled by them.
- 12% of pediatric inpatients possibly suffer from chronic pain.

Catastrophizing [“Awfulizing”]

- A set of negative emotional/cognitive processes such as magnification, rumination and pessimism about pain sensations and feelings of helplessness when in pain.
- Significant link between child and parent catastrophizing.
- Catastrophizing delays analgesic effectiveness of distraction.
- Assessment Tool: Pain Catastrophizing Scale-child version.

Chronic Pain in Children

- Pain lasting > 3-6 months: Time definition arbitrary
- Pain that extends beyond the expected period of healing and hence lacks the acute warning function of physiological nociception


Fear of Pain

- Plays a significant role in relation to functional disability and depressive symptoms in the context of pediatric chronic pain.
- Appears to play both a facilitative and inhibitory role in relation to treatment response:
  - May hinder improvements in disability & depressive symptoms
  - Declines are strongly associated with positive functional outcomes

Chronic Pain Pathophysiology

- Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders.
- Considerable evidence, especially from twin studies, points to a role of shared biological sensitivity: "pain vulnerability", "pain sensitivity", or "central sensitivity syndrome."

Chronic-on-acute Pain

- Approximately 5% of children and teenagers in general population have significant pain related dysfunction.
- In USA: > 3.7 million children
- At least (!) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, or cancer are expected to display chronic pain in addition to their underlying somatic pain episode.

Communication with Patient / Family

- Pain is real!
- First: "function" gets better, then "pain" (not other way around)
- Positive Expectation = Self-fulfilling prophecy

Communication with Patient / Family

- Physical Therapy
  - Daily home exercise

Weight bearing 1 second

Running Marathon
Communication with Patient / Family
What is the Hard Work...and non-negotiable...?

- **Physical Therapy**
  - Daily home exercise
- **Integrative Medicine**
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation, etc.
  - Daily home exercise
  - Passive: Massage, Acupuncture
- **Psychology**
  (...if missing school, anxiety, depression...)

Deep Breathing

Self-Hypnosis

Coping Skills

CBT

DBT

Inpatient Psychiatric Hospitalization

Communication with Patient / Family
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  (...if missing school)
- **Normalize Life**
  - Sports/Exercise
  - Sleep-hygiene
  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)

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  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)
- **Family Coaching**
- **Medications...???
Medications ??

1. Low-dose Amitriptyline (stimulates Opioids in the absence of tissue injury or inflammation not indicated!
2. Gabapentin (inhibits)
3. Acetaminophen
4. Ibuprofen (Celecoxib?)
5. Lidocain 5% patch
6. Melatonin
7. Vitamin D ?
8. SSRI ?
9. Co-Q10, Fish-Oil/Omega 3000, Peppermint oil (coated) [for abdo pain]? Exit Interview

Conclusions Acute (!) Pain

• Pain is, when the child says so
• Use multimodal (opioid-sparing) analgesia
  - incl. combination of integrative methods, rehabilitation and anesthetic medications
• Include 4 WHO Principles

Pain in the absence of tissue injury or inflammation not indicated!

Conclusion chronic-on-acute pain

• Many clinicians have historically considered most chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation), and data increasingly suggest this is simply not the case
• Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders

Close collaboration with specialist of underlying acute condition to ensure no injury will be caused by pain rehab treatment
• Opioids in the absence of tissue injury or inflammation are contraindicated!
• Importance of rehabilitative, interdisciplinary team approach

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

Physician
• Kaci Osege, MD
• Kris Camire, MD
• Kathleen Forky, MD
• Stefan Friedrichsdorf, MD
• 2 Fellows

Nurse Practitioner
• Burk Symala, RN, CNS
• Nancy Jaworski, RN, CNS
• Kathy Papp, RN, CNS
• Sarah Tho, RN, CNS
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• Jennifer Worley, RN, CNS

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• Christine Gibson, LP, PhD
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• Leslie Quast
• Laura Fout
• Julie Yang

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• Michael McGuire

Social Work
• Janet Schanier LCSW
• Cynthia DiGennaro

Music Therapy
• MarkBurnett

Chaplain
• Hal Weiden

Child Life
• Margaret Manuson

Clinic nurse
• Blanche Amar

Manager
• Kristi McQuade

Clinic nurse
• Tracy Crofut
• Lu Legerston, RN

ossip in the absence of tissue injury or inflammation not indicated!

Children’s MINNESOTA

Further Training:
CIPPC@ChildrensMN.org

9th Annual Pediatric Pain Master Class
• Minneapolis, MN | June 11-17, 2016

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatric Trainer
• 9th Conference: Chicago, IL | March 12-13, 2016
http://tinyurl.com/EPEC2016

Thank you so much!

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Medical Director, Department of Pain Medicine, Palliative Care & Integrative Medicine
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Ave S | Minneapolis, MN 55404 | USA
612.813.6450 phone | 612.813.7199 fax
stefan.friedrichsdorf@childrensMN.org

http://www.childrensmn.org/services/painpalliativeintegrativemed

Blog: http://NoNeedlessPain.org

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612.813.6450 phone | 612.813.7199 fax
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ADDENDUM

Further Reading

Conquering Your Child’s Chronic Pain
A Pediatrician’s Guide for Reclaiming a Normal Childhood
Lorraine K. Zeitner, M.D.
HarperResource
$ 14.95

Recommended Reading

• The mystery of chronic pain https://www.youtube.com/watch?v=J6--CMhcCfQ

PainBytes


Persistent (Chronic Pain)

http://www.youtube.com/watch?v=88dL73206dE&feature=youtu.be

Most Muscles, bones, ligaments and discs are healed by 3 to 6 months.
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, smart-phone/tablet “apps”)
  - Acupressure, acupuncture, aromatherapy

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)

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
NSAIDs for Neuropathic Pain

- No RCTs for amitriptyline, nortriptyline, desipramine, or imipramine.
- Preclinical and clinical studies have demonstrated efficacy for NSAIDs in neuropathic pain states.
- Tricyclic antidepressants (TCA)

Opioids for Neuropathic Pain

- Morphine, oxycodone NNT 4.3; NNH 11.7
- Tramadol NNT 4.7; NNH 6.3
- Tapentadol? Bias; NNT 10.2

Amitriptyline

- NNT: 3.6; NNH: 13.4
- No dose-response effect
- Efficacy of TCA in central pain: meta-analysis of randomized controlled trials showing that TCA are effective in relieving central pain.

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.
- 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.

Diclofenac-Patch

- NSAID
- Analogic action of topical diclofenac: peripheral NMDA receptor antagonism.

Amitriptyline (or Nortriptyline)

- Adverse effects: arrhythmia: EKG (Q-Tc, WPW?), anticholinergic (dry mouth, constipation, blurred vision, sedation)
- Desipramine: anecdotal evidence of sudden death in children

Chronic pain: underutilization of effective treatments.
**Nociceptive Pathways & Primary Sites of Action of Analgesics**

- **Tricyclic Antidepressants:** (+) Opioid analgesia via serotonergic mechanism at brainstem

**Gabapentin**

- **Gabapentin:** NNT: 6.3; NNH: 25.6
- **Extended-release gabapentin:** NNT 83; 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 neuropathic pain 2.9: post herpetic neuralgia 3.9**

**Pregabalin**

- **Efficacy worse than gabapentin**
- **NNT: 7.7; NNH: 13.9**
- **Dose-response (600mg/day more effective than 300mg/day)**
- **Linear (pregabalin) versus non-linear (gabapentin) bioavailability:** Clinical relevance unclear.

**Children with impairment of CNS**

- **Gabapentin appears to be an effective treatment for children with severe impairment of the CNS and recurrent pain behaviors, including intermittent changes in muscle tone.**
  - **Age range:** 5 months - 5 years
  - **Greater than or equal to 6 years:**
  - **Average daily dose:**
    - 50 mg/kg/day (42-72 mg/kg/day)
    - 36 mg/kg/day (32-40 mg/kg/day)
  - **Suggested guidelines:**
    - Initial half 25-40 mg/kg/day
    - Increase up to 50-70 mg/kg/day in those <6 years

**Gabapentin for Acute Pain?**

- **Total knee replacement:** Decreased post-op opioid use, improved functional recovery
- **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
- **Type of clinical condition may influence effectiveness of combination drug therapy**

**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

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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

- Most studies negative:
  - Poorest safety profile:
    - Topiramate NNT 6; NNH 6.3
    - Zonisamide NNH 2.0
  - Oxcarbazepine / carbamazepine NNH 5.5

Nociceptive Pathways & Primary Sites of Action of Analgesics

- 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)
    - Antinflammatotry
    - Directly lyse some tumors (e.g. lymphoma)
    - Prostaglandin inhibition - direct analgesic effect
  - 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
  - Malignant spinal cord compression (adult dose):
    - Dexamethasone (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):
    - Dexamethasone 16-96 mg/day or equivalent
  - Dosage iv/po: Dexamethasone (glucocorticoid): 0.1 - 1.5 mg/kg (max. 10mg) starting dose, then 0.1 - 0.25 mg/kg x2/day (for < 14 days)
  - Use gastroprotective agent (!)
Sodium channels are involved in pain...

- After nerve injury, expression of some Na⁺ channels increases de novo, the expression of others diminishes, and some translocate into different cellular compartments
- The proliferation of heterotopic sodium channels, such as Nav1.3, Nav1.7, and Nav1.8, may lower the stimulation threshold and provoke ectopic discharge, resulting in spontaneous pain.

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?)

IV Lidocaine - Pediatric Experience

- Nausea after 4 days?
- Neuropathic 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
- Case Series (n=5) after anti-GD2 antibody therapy in children with neuroblastoma
- Case report: end-of-life cancer care: 2.1-3 mg/kg/hr
- Side Effects: Nausea, hallucinations, muscle twitches, seizures
- Case report: 5-year-old patient with neuropathic cancer 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%
- Oral mexiletine, tocainide, flecainide: High side effect liability from oral drugs: Not recommended
- How about local lidocaine and novocaine...?

Magnesium as Analgesic?

- 2007: systematic review, no analgesic evidence (postoperative, adjuvant)
- 8 RCTs spinal Mg: lower pain scores & analgesic requirements
- Administration: IV (severe hypo-Mg), PO (mild)
- Theraeputic Review 2013
- 13 RCTs, all but 2 reported reduced postop pain & analgesic requirements
Analgesic (subanesthetic)

- Racemic mixture \([S(+)-\text{enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]\)
- Sedative-Hypnotic-Dissociative
  - PO: 0.2-0.5 mg/kg TID-QID and PRN (sc, sl, intransal, pr, spinally)
  - Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??

Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture \([S(+)-\text{enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]\)
- Dosing
  - IV: 1-5 mcg/kg/min
  - Analgesic (subanesthetic) Dosing: IV: 1-5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
  - Intravenous infusion in refractory cancer pain: considerations about the increased risk for ketamine induced hallucinations (euphoria, dysphoria, vivid hallucinations)
  - No psychotropic side effects, no sedation. Ketamine has been marketed as a non-sedative analgesic for cancer pain (with or without lidocaine).

Low-dose Ketamine

- Action which may contribute to analgesic effect:
  - PO: 0.2-0.5 mg/kg TID-QID and PRN (sc, sl, intransal, pr, spinally)
  - Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??
  - No psychotropic side effects, no sedation. Ketamine has been marketed as a non-sedative analgesic for cancer pain (with or without lidocaine).

Low-dose Ketamine - Adult Evidence

- Metaanalysis: NMDA antagonists (\(\mu\)- and \(\kappa\)-opioid-like effect) have no consistent clinical relevant efficacy in neuropathic pain [Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2007; 8(6):515-21]
- No psychotropic side effects, no hallucinations

Low-dose Ketamine - Pediatric Evidence

- 5-year-old girl, meningitis caused by malignant T-cell lymphomas caused with difficult to treat neuropathic pain.
  - IV (2 mcg/kg/min) and later ketamine (2 mcg/kg/min) in combination with fentanyl (0.9-1.2 mg/kg/hr) provided good analgesia without significant side effects for the last 20 days of her life.

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.
  - RCT (n=60): Adult CRPS patients - 4 day low-dose (1.2-7 mcg/kg/min) infusion reduced pain scores week 1-11 (not 12) without functional improvement. Kepner PE et al. Ketamine produces allodynia and long-term pain relief in patients with Complex Regional Pain Syndrome Type I. Pain 2009 Apr;145(1): 186-191.
  - Metaanalysis: NMDA antagonists (\(\mu\)- and \(\kappa\)-opioid-like effect) have no consistent clinical relevant efficacy in neuropathic pain [Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2007; 8(6):515-21]
Ketamine

- Estimated at 1:1 - 1:3 (i.e. 1mg IV = 1-3 mg PO)
- Steady-state oral/parenteral ratio unclear
- Bio-availability 93% IM/IV; 20% PO
- 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

Other Adjuvant Analgesics / Co-analgesics

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.

α-Adrenergic Agonists

- Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory G-proteins
- Presynaptic alpha-2-adrenoceptors 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 pontosomal noradrenergic inhibitory system
α-2-Adrenergic Agonists: Clonidine vs Dexmedetomidine

- **Dexmedetomidine** has greater α2- versus α1- selectivity than clonidine.
- **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).
- **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

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.
- **Children of Minnesota**: Dose 1 mcg/kg/hr titrated to effect up to 3 mcg/kg/hr (Athens, Greece 5/16/2014).

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).

Dexmedetomidine

- **n=107 patients**, age 3 days-17 years, retrospective review.
- Dexmedetomidine, as part of multi-modal review, 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]
- **Withdrawal effects** were noted in patients following prolonged infusion.

Cannabis

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

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**References**

Cannabis

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


- 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

**Cannabis**

**Correlation with mental illness**


**Impairment of driving ability**

**Health issues associated with cannabis**

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

**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.


**Cannabinoids**

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

**Positive Effects**

**Cannabidiol (CBD):**

- Youths exposed to cannabis and prescribed psychotropics for cannabis-related disorders
- 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)

**Negative Effects**
Other Adjuvant Analgesic / Co-analgesics

- Muscle relaxants: Baclofen; Cyclobenzaprine (Flexeril®)
- Bisphosphonates: Osteoclast inhibitors -> metastatic bone pain
- Antispasmodics: Hyoscine butyl bromide (Buscopan®) [not in USA], hyoscyamine (Levsin®), oxybutynin (Ditropan®), glycopyrrolate (Robinul®)
- Anti-TNF α agent [treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpAs)]
- Back Pain: Adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi)
- Osteoarthritis: Etanercept (Enbrel), golimumab (Simponi)
- Statins: Mouse: simvastatin, rosvustatin prevented injury induced neuropathic pain

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

Botulinum toxin A

- Peripheral neuropathic pain
- 6 RCTs: 50-200 units s.c. in the region of pain
- Low placebo effect
- NNT: 1.9 [95% CI 1.5-2.5 for 4 studies]: one large (unpublished) study negative

Further Reading:

Thank you very much!