The Presidential Plenary: “Pain Management”

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Pain after burn injury: Multifactorial

- **Acute Pain**
  - Tissue damage, repetitive trauma
- **Procedural Pain**
  - Dressing changes, Intravenous access
- **Neuropathic Pain**
- **Psycho-spiritual-spiritual Pain**
- **Chronic Pain**
  - Pain can persist after healing
  - n=358; burns covering an average of 59% of their bodies
  - 12 years later: 52% of respondents reported ongoing burn-related pain

- Discuss the four WHO-principles of **acute pain** management & review concept of multimodal analgesia
- Review the evidence for importance of managing **procedural pain** (from IV access to dressing changes): topical anesthesia, positioning, and distraction (e.g., sucrose if <12 months) plus/minus sedation
- Appreciate high prevalence of **neuropathic pain** in patients with burn injuries and discuss a step-by-step treatment approach
Today's Presentation

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

Pediatric Pain - Status Quo

+ Under treatment of pain in children
+ Parents expect pain to be relieved
+ Parents’ greatest distress: failing to protect their child from pain
+ Assumption: everything possible is done

Pediatric Pain - Status Quo

+ USA: adults receive more than two - three times as many analgesic doses as children (with identical diagnoses)
+ Compared to adults, pediatric patients receive fewer and/or incorrectly dosed analgesics in daily routine
+ The younger children are, the less likely they receive appropriate analgesics

For example:
- Beyer JE, DeGood DE, Ashley LC, Russell GA. Patterns of postoperative analgesic use with adults and children following cardiac surgery.
Inappropriate Analgesia: Why Bother...?

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression. The Medical Research Council and 1946 National Child Development Study.


- Trauma & post-traumatic stress disorder (PTSD)


Myths and Barriers to Using Opioids?
Assumptions #1: Addiction

- **Addiction** → a chronic relapsing condition characterized by persistent, compulsive dependence on a behaviour or substance despite adverse consequences
- **Withdrawal** → distressing symptoms occur if opioids discontinued or tapered too fast (or opioid antagonist given)
- **Tolerance does NOT equal addiction**
- **Tolerance** → Decrease in drug effect as result to prior exposure to the drug (for analgesia and/or adverse effect)
- **Beware of “Pseudo-addiction”**

Assumptions #2: Over-Sedation

- **Misconception that goal of opioid use is to sedate**
- **Patients/Parents do NOT have to choose between poor pain control or over sedation**
- **Goal is to provide excellent symptom control (pain, dyspnea) while maintaining function**
- **Over sedation / Drowsiness / desaturation is occasionally experienced after opioid initiation or dose increase**
  - **Good analgesia**: decrease dose
  - **Poor analgesia**: opioid rotation

Common Opioid Assumptions

- **Addiction**
- **Over Sedation / Respiratory Depression**
- **Ileus / Gut hypomobility / Constipation**
- **Medication “Too strong”**
- **Masking symptoms: Abdominal Pain**
- **Opioids after major cranial surgery in children do NOT result in altered mental status nor respiratory depression**
- **As always... Think first (compartment syndrome?)... analgesia second... Masking symptoms**
How Do We Manage Acute Pain in Children?

No Needless Pain

That’s why we’re called

No Needless Pain

Multimodal Analgesia

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses


- Dosing at regular intervals (“By the Clock”)
- Adapting treatment to the individual child (“With the Child”)
- Using the appropriate route of administration (“By the appropriate route”)
- Using a two-step strategy (“By the Analgesic Ladder”)

✤ Dosing at regular intervals (“By the Clock”)
✤ Adapting treatment to the individual child (“With the Child”)
✤ Using the appropriate route of administration (“By the appropriate route”)
✤ Using a two-step strategy (“By the Analgesic Ladder”)
WHO Principle 1: Dosing at Regular Intervals

- 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 “PRN”) basis
- Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN ("as needed") dosing
- PRN = Patient Receives Nothing

- 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

Switching Opioids

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

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

Pain Assessment

- Patients simultaneously may experience different qualities, including
  - Nociceptive Pain
  - Somatic Pain
  - Visceral Pain
  - Psycho-social-spiritual Pain (“Total Pain”)
  - and/or Neuropathic Pain
  - and/or Chronic Pain

- Be creative when measuring pain: a single pain score often will not be enough:

Regular (!) Pain Assessment

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

Route of Administration

- Analgesic Drugs
  - Oral
  - Intramuscular (I.m.)
  - Intranasal (MAD device)
  - Sublingual
  - Transmucosal
  - Transdermal
  - Suppository
  - Nebulization
WHO Principle 4: Using a Two-Step Strategy

WHO Step 1
Mild Pain

Ibuprofen and/or Acetaminophen (Paracetamol)

Other NSAIDs?
Cox-2 Inhibitor?

Citius, Altius, Fortius...?

Ibuprofen salts: fast-acting formulations

* produced significantly better analgesia over 6h, fewer re-medications than standard formulations

* 200-mg fast-acting ibuprofen (NNT 2.1; 95% confidence interval 1.9-2.4) was as effective as 400 mg standard ibuprofen (NNT 2.4; 95% CI 2.2-2.5), with faster onset of analgesia.

More rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events.

However, earlier onset preferred in other pain condition, such as chronic nociceptive or neuropathic pain?

Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

NSAIDs

Acetaminophen (Paracetamol)

Thalamus
Brain Regions that Modulate Pain and Emotion

- Somatosensory Cortex
- Insular Cortex
- Thalamus
- Hippocampus
- Amygdala
- Prefrontal Cortex
- Anterior Cingulate Cortex

**WHO Principle 4: Using a Two-Step Strategy**

**WHO Step 1**
Mild Pain
- Ibuprofen
- and/or
- Acetaminophen (Paracetamol)
- Other NSAIDs?
- Cox-2 Inhibitor?

**WHO Step 2**
Moderate to Severe Pain
- Morphine
- or
- fentanyl,
- hydromorphone,
- oxycodone,
- methadone

**Morphine Pharmacokinetics**

- “A principle of pharmacokinetics teaches us that unless the drug reaches the site of action, it cannot be expected to exert its dynamic effect.

- With morphine the situation is that when the drug dose not reach the PATIENT, what hope is there for pain relief?”

Ghooi & Ghooi: Lancet 1998; 325:1625
WHO Principle 4: Using a Two-Step Strategy

**WHO Step 1**
Mild Pain

- Ibuprofen
- and/or
- Acetaminophen (Paracetamol)
- Other NSAIDs?
- Cox-2 Inhibitor?

**WHO Step 2**
Moderate to Severe Pain

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

**Intermediate Step?**
- Tramadol
- Codeine
- Hydrocodone

Cytochrome P450 2D6

**Current body of evidence cannot support whether the main analgesic effect results from hydrocodone or the metabolite hydromorphone.**


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

**Opioids**
- Pre-synaptic nerve terminal
- Neurotransmitter release
- Post-synaptic nerve terminal: Membrane hyperpolarization
- \( \Rightarrow \) suppress neuronal excitability

**Acetaminophen (Paracetamol)**

**NSAIDs**
Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

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

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

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
How does this stuff work...?

Distraction significantly increased the activation of the cingulo-frontal cortex including the orbitofrontal and perigenual anterior cingulate cortex (ACC), as well as the periaqueductal gray (PAG) and the posterior thalamus. Active distraction techniques, such as imagery, appear to modulate endorphine release in the midbrain, including the periaqueductal gray and thereby increase activity of descending inhibiting pathways thereby decreasing nociception from the dorsal horn resulting in gate pain modulation during distraction.1-4

Today’s Presentation

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

Procedural Pain in Children: From IV access to dressing change

Procedural Pain Management

5-year Marius requires stitches in ED
Procedural Pain: A call for action

- What are children most afraid of coming to our clinical service?
- Needle procedures (incl. vaccine injections) performed in childhood are a substantial source of distress
- It is estimated that up to 25% of adults have a fear of needles


Pain outcomes in a US children’s hospital: a prospective cross-sectional survey

- In past 24 hrs, what was cause of worst pain?
  * 40% Needle poke
  * 34% Trauma/injury/other medical
  * 10 % Surgery
  * 8% Procedure
  * 4% Acute illness/infection
  * 3% Treatment for known disease


Procedural pain: A call for action

- Pain ratings at 4-6 months routine vaccination higher for circumcised versus uncircumcised boys S Taddio A (1994) Lancet, 344:291-2


- Memory of previous painful experience has great influence on pain experience during subsequent procedures Verduijn J, Noordam-Stigter HJ, Hoogenboom J. Children’s self-reported pain at the dentist. Pain 2008;137:589-94

Essential Components of Procedural Pain Management

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

Other Considerations
- Possibly other pharmacological approaches
- Consider appropriate sedation, if excellent analgesia cannot be achieved

“Non-negotiable” Components of Procedural Pain Management in Children

1. Numbing
2. Sucrose
3. Positioning
4. Distraction
Topical Local Anesthetics


- Topical anesthetics are considered safe for children of all ages. However, administration of excessive doses and/or prolonged application times can lead to serious adverse effects, including irregular heartbeat, seizures and difficulty breathing. www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2009/emla_ametop_pc-cp-eng.php

- For children undergoing vaccination, there is insufficient evidence for or against the use of skin-cooling techniques (vapocoolants, ice, cool/cold packs) to reduce pain at the time of injection (grade I recommendation, based on conflicting level I evidence).

EMLA versus LMX

- EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) vs Ela-Max LMX 4% Lidocaine Topical Anesthetic Cream

- Ela-Max LMX: 30 minutes application as effective as 60 minutes

- EMLA application for preventing pain during IV insertion in Children

- Analgesia duration:
  - EMLA 1-2 hours vs. LMX 1 hour

- Skin time:
  - EMLA 4 hours vs. LMX 2 hours

EMLA® and Neonates

- In neonates, EMLA reduces the behavioral pain response to venipuncture but not heel lance

- Single doses have not been associated with methemoglobinemia

- Effective for neonates > 34 weeks gestation for lumbar puncture
Application of Cream

- Cellophane (no Tegaderm®: hurts at time of removal)

Needle pokes without the pain?

J-Tip in the Emergency Room (CBS 4 Morning News)

J-Tip (Lidocaine)

- J-tip: single-use, disposable, carbon-dioxide-powered, needleless lidocaine injector
- Adults: More pain than s.c. lidocaine

LET Anesthesia

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

“Non-negotiable” Components of Procedural Pain Management in Children

Sucrose for Children 0-12 months

- Reduces pain (PIPP, VAS) and cry during painful procedure, such as venipuncture
- Role of endogenous opioids - naloxone blunts effect
- Effective dose (24%): 0.05 - 0.5 mL (= 0.012 - 0.12 g)
- Administration 2 minutes prior to mild - moderately painful procedure
- Duration ~ 4 min
- Does not prevent development of hyperalgesia
- Breastfeeding
  - Effective in term infants (superior to sweetening agents)
“Non-negotiable” Components of Procedural Pain Management in Children

3. Positioning

Pediatric Positioning in 1985

* When feasible, offer choice to child (parent’s lap?)

Comfort Positioning

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


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

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

Integrative Therapies for Needle Procedures


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

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

Integrative Therapies for Needle Procedures


- Parent coaching: Certain types of parental behaviours (e.g., nonprocedural talk, suggestions on how to cope, humour) have been related to decreases in children’s distress and pain, whereas others (e.g., reassurance, apologies) have been related to increases in children’s distress and pain. Taddio A, Chambers CT, Holterman SA, et al. Inadequate pain management during childhood immunizations: the nerve of it. CMAJ Ther 2009;9(Suppl 2):S52-67.

- Integrative Therapies for Needle Procedures
Distraction

- Reduction of fear and anxiety
- Determine if the child wishes to watch or be distracted
- Young children: books, bubbles and pinwheels
- Coaching roles for parents
- Older children: video games and biofeedback
How many mistakes can you spot?

New York Times 7/2/14: The Price of Prevention: Vaccine Cost

“Non-negotiable” Components of Procedural Pain Management in Children

Other Considerations

(5) (Intranasal) Systemic Analgesia
(6) Sedation

Intranasal Opioid Application

- Nasal mucosa richly vascularized
- Fenestrated epithelium drains by way of the facial and sphenopalatine veins
- ⇒ Avoiding first pass metabolism

- Hydromorphone: ER trauma patients - plasma concentration similar to those after IV administration
Intranasal Opioid Application

- Drops or spray diluted in normal saline 0.9%
- Pharmacokinetic profile similar to i.v. in children
- Mucosal Atomization Device (MAD)

- RCT
- 24 children (4-8 years)
- Burn dressing changes
- Control: oral morphine
- Titrated until pain free
  - intranasal dose slightly higher (1.4 mcg/kg + 15mcg Q5min)
  - pain relief comparable
  - safety profile acceptable, no serious adverse events


Intranasal Opioid Application

- RCT
- 32 children (4-8 years)
- Postoperative analgesia
- Control: i.v. fentanyl
- Titrated until pain free
  - intranasal dose slightly higher (1.4 mcg/kg)
  - pain relief comparable
  - safety profile acceptable, no serious adverse events


Intranasal Opioid Application

- Case report
- Acute pain ER
- 48 children (3-12 years)
- Dose applied every 5 minutes as required
- Median dose: 1.5 mcg/kg
  - good pain control
  - no side effects

If good procedural analgesia not feasible with the “4 Non-Negotiables”, consider:

(1) Mild sedation: Nitrous gas

or

(2) Moderate/deep sedation (e.g. ketamine, propofol)

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

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

Pain after burn injury


  - n=358; burns covering an average of 59% of their bodies
  - 12 years later: 52% of respondents reported ongoing burn-related pain

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)
Neuropathic Pain Assessment

- Currently there are no validated neuropathic pain scales for children < 18 years
- Adults
  - NPS® Neuropathic Pain Scale - 12 items
    - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm)
  - Pain Quality Assessment Scale (PQAS) - 20 items
    - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm)

Pain Quality Assessment Scale (PQAS) - 20 items

- NSAIDs for Neuropathic Pain
  - NSAIDs are so widely viewed as being ineffective for neuropathic pain that no major guidelines even mention them in their algorithm.
  - Preclinical and clinical studies have demonstrated efficacy for NSAIDs in neuropathic pain states

Opioids for Neuropathic Pain

- Adult Evidence: Metaanalysis: Opioids, including tramadol, have a consistent efficacy in neuropathic pain
  - Multi-mechnism agent
    - Tramadol: RCTs: polyneuropathy and post-amputation pain
      - Wilder-Smith, Anesthesiology 2005, 103:616-28

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

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Neuropathic Pain Mechanisms

- **Thalamus**
- **Central Sensitization:**
  - Activities in C-Fibers drives changes in 2nd neuron
  - Gial activation & cytokine release also involved?
  - Result: excitability and synaptic efficiency
- **Injury Induced Accumulation of Na-channels**
  - Tropical pain
- **Peripheral Sensitization:**
  - Response to Tissue Injury

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Tricyclic antidepressants (TCA)

- 61 RCTs (20 antidepressants):
  - TCAs are effective; NNT of 3.6 (for the achievement of at least moderate pain relief)

- No effect of amitriptyline in HIV neuropathy:

- Secondary amine TCAs (e.g., nortriptyline) better tolerated than tertiary amine TCAs (e.g., amitriptyline) with comparable analgesic efficacy

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Amitriptyline

- Dosage: initial 0.1 mg / kg -> titrate to 0.4 mg / kg p.o., [max. 20-25 mg] (usually not up to 1-2 mg / kg / day) once at night -
  - wean: decrease gradually!
- Effect: days - weeks; depends on length of symptoms

- Adverse effects: arrhythmia: EKG (QTc, WPW?), anticholinergic / antihistamine (dry mouth, constipation, blurred vision, sedation)

- Desipramine: anecdotal evidence of sudden death in children

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Nociceptive Pathways & Primary Sites of Action of Analgesics

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

- Gabapentinoids: Ca-channel α2-δ ligands

  - Voltage-gated Ca-channel
  - presynaptic nerve terminal
  - Postsynaptic nerve terminal
  - Glutamate
  - Substance P

  - α2-δ subunit [dysfunction/upregulation role in neuropathic pain]
Gabapentinoids


  - 42% improved compared to 19% on placebo
  - NNT for effective pain relief in diabetic neuropathy 2.9; post herpetic neuralgia 3.9

- **Pregabalin**: Effective in post herpetic neuralgia, painful diabetic polyneuropathy, central neuropathic pain (19 studies, 7003 participants); effective 300 mg-600 mg daily (at 150 mg daily was generally ineffective). Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009 Jul 8; 1(DCD007079).

  - No overall evidence for superior efficacy for either of these drugs in neuropathic pain, although lower cost may favor gabapentin

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

Analgesic adjunct in the immediate postburn period


Gabapentinoids: Ca-channel α2-δ ligands

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

Gabapentin 300 mg TID ➔ Gabapentin 900 mg / day ➔ Pregabalin 150 mg / day ➔ Pregabalin 75 mg BID

Nociceptive Pathways & Primary Sites of Action of Analgesics

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

- Integrative (non-pharmacological) therapies

- TCA SSRI Methadone Tramadol

- Combination: Amitriptyline & Gabapentin

Sodium Channel Blocker: Topical Lidocaine

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

- Oral mexiletine, tocoainde, flecaainide are analgesic in neuropathic pain: High side effect liability from oral drugs; generally considered third-line

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

- Efficacy of IV lidocaine supported by RCTs

[References]


As current clinical evidence is based on only one RCT as well as case series and reports, intravenous lidocaine must be considered a pharmacological agent under investigation in burns care, the effectiveness of which is yet to be determined with further well-designed and conducted clinical trials.


Opioid induced tolerance and hyperalgesia

- Opioid
- mu-receptor
- uncoupling
- stimulation
- generation
- Protein Kinase-C
- Other neuromodulators
- Inhibition of Ca channels: neurotransmitter release
- Alter characteristics of neuron => suppress neuronal excitability
- Membrane Hyperpolarization (K+ channel)

NMDA-Receptor Channel Blocker

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

Excitatory NMDA (N-Methyl-d-Aspartate) 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

NMDA-Receptor Channel Blocker

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

- **Sedative-Hypnotic-Dissociative**
  Dosing: 1-2 mg/kg/dose IV

- **Analgesic (subanesthetic)**
  Dosing: IV: 1-5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
  - Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??

- 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. Postoperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004603

- **Metaanalysis:** NMDA antagonists (& mexiletine) have no consistent clinical relevant efficacy in neuropathic pain Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep; 150(3):573-81.

- 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

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

- **Sensory-Selective (Nociceptive-Selective) Nerve Blockade**

These adjuvant analgesics/co-analgesics may be beneficial in certain clinical scenarios, but their specific indications and contraindications should be considered based on individual patient needs and medical history.
Nociceptive Pathways & Primary Sites of Action of Analgesics

**Thalamus**

**Periaqueductal grey (endorphins)**

**Integrative (non-pharmacological) therapies**

**NSAIDs**

**Injury**

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

**Opioids**

**Acetaminophen (Paracetamol)**

**TCA SSRIs Methadone Tramadol**

**Stimulation of inhibiting GABA system**
- Baclofen
- Benzodiazepines Valproate

**Descending inhibition**

**Integrative (non-pharmacological) therapies**
- TCA SSRIs Methadone Tramadol
- Acetaminophen (Paracetamol)
- **NSAIDs**

**Role of Cannabis?**

San Diego, CA

**AAP Handout for parents**

"Despite relaxed regulations, marijuana harms developing brain":
http://aapnews.aappublications.org/content/36/3/4.full.pdf+html

**Updated AAP policy opposes marijuana use, citing potential harms, lack of research**
http://aapnews.aappublications.org/content/early/2015/01/26/aapnews.20150126-1

**Resources**
- Chain reactions, pain chemistry (courtesy of S. Davis)
- Pain database (courtesy of University of Washington)
- Pain clinic (courtesy of Stanford University)
- Pain management (courtesy of University of California)
- Pain management (courtesy of Johns Hopkins University)
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 PPC


  - central neuraxial infusions
  - peripheral nerve and plexus blocks or infusions
  - neurolytic blocks
  - implanted intrathecal ports & pumps for baclofen, opioids, local anesthetics, and other adjuvants
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; manage comorbidities (anxiety, sleep disturbances)
3. Opioid (plus non-opioid) analgesics [consider Tramadol or Methadone]
4. Tricyclic Antidepressant (or Ca-channel α2-δ ligand) ± ketamine
5. Tricyclic Antidepressant and Ca-channel α2-δ ligand
6. Lidocain patch (if localized pain)
7. NMDA-receptor-channel blocker [benzodiazepine? α-agonist? IV lidocaine?]
8. Regional anesthesia

Conclusions Pain

- Use multimodal (opioid-sparing) analgesia  
  - incl. combination of integrative methods, rehabilitation and analgesic medications
- Patients/Parents do NOT have to choose between poor pain control or over sedation
- Opioids should NOT be administered long-term
- Opioids NOT indicated for chronic pain
- Treatment protocol for painful procedures is expected standard of care in 21st century:
  - positioning, topical anesthesia, integrative therapies, sucrose
- Neoplastic pain often under-assessed and under-treated
- Careful step-by-step approach (combining integrative, rehabilitative, pharmacological and interventional therapies) warranted
- First Line medications: Opioids (?), Amitriptyline, Gabapentin
- Low-dose Ketamine may represent a potent adjuvant analgesia
- plus/minus sedation; systemic anesthesia
ADDENDUM

Non-Opioids ("Simple" Analgesia)

- **Acetaminophen (Paracetamol)**
  - 10-15 mg/kg PO/PR Q4-6h; dose limit: <2 years: 60mg/kg/day, >2 years: 90mg/kg/day, max. 4g
  - FDA 2013: max. 650mg/dose; max. OTC (!) 2.6-3mg/day
  - Generally well tolerated
  - Lacks gastrointestinal and hematological side-effects
  - Has to be watched for rare hepatotoxic side effects
  - (0-6 months of age) was associated with allergic sensitization/history of asthma in girls at 10 years of age

- **Ibuprofen**
  - 5-10mg/kg PO TDS-QID; dose limit 2400mg/day
  - Least gastrointestinal side effects among the NSAIDs
  - Caution with hepatic or renal impairment, history of GI bleeding or ulcers
  - May inhibit platelet aggregation
  - Acetaminophen (Paracetamol) & Ibuprofen can usually be used in combination, e.g. scheduled Q6h administered at the same time!

- **Ketorolac (Toradol®)**: < 2 years: 0.25 mg/kg i.v.; > 2 years: 0.5 mg/kg i.v., max. 30mg, max. 5 days

Meta-analysis (30 studies, 2364 patients): IV acetaminophen reduces postoperative nausea and vomiting

Opioid Sparing

- RCT Postsurgical pediatric patients: NSAID vs placebo, with parenteral opioids as rescue analgesics, the NSAID groups typically show lower pain scores and a 30% to 40% reduction in opioid use. Vetter T, Heiner E. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine.

Case Example 1: Andrea

- 10-year-old girl in severe acute pain (e.g. metastasized osteosarcoma, sickle cell crisis); weight: 20 kg
- PCA pump currently not available
- Choice of opioid?
  - Immediate release morphine
  - ...unless...

Case Example Morphine

- Route of administration?
- Per kg dosing: Maximum 50 kg
- Lean weight for obese children
- Please write the order (small group work)
Case Example Morphine (Immediate Release)

- **Scheduled (round-the-clock) dose**
  - IV: 0.1 mg x 20 kg = 2 mg Q4h (= 12 mg/day)
  - PO: 0.3 mg x 20 kg = 6 mg Q4h (= 36 mg/day)

- **Breakthrough (rescue) dose** = 1/10 - 1/6 of daily dose (Q1-2h)
  - IV: (1.2 - 2 mg) 1.2 mg Q1h PRN
  - PO: (3.6 - 6 mg) 3.6 mg Q1h PRN

- if pain score > ...?.../10 and no signs of over sedation

Case Example: Sean

- 10-year-old boy in severe acute (!) pain (e.g. metastasized osteosarcoma, sickle cell crisis); weight: 20 kg
- PCA pump now available

**Question:** PCA bolus only or continuous infusion plus PCA bolus?

**Meta-Analysis:** Addition of continuous (or background) infusion to the demand (or PCA bolus) dose for IV-PCA is NOT associated with a higher incidence of respiratory events than PCA bolus alone in pediatric patients (in contrast to adults).


Opioid Dose Escalation for Acute (!) Pain

- How to increase the dose?
- 50 per cent rule!

“It Depends” - Socrates
Please write PCA Order

- Morphine (and Plan B: Fentanyl and Plan C: Hydromorphone)
- Patient (or nurse-) controlled analgesia: PCA
  - (1) Continuous Infusion
  - (2) PCA- Dose
  - (3) Lock-Out Time
  - (4) Maximum number of boluses per hour

Continuous Infusion / PCA Dose

- (1) Background (continuous) infusion i.v/s.c.:
  - Morphine: 15-20 mcg x 20 kg = 0.3-0.4 mg/hr
  - Fentanyl: 0.5-1 mcg x 20 kg = 10 - 20 mcg/hr
  - Hydromorphone: 2-5 mcg x 20 kg = 40 - 100 mcg
- (2) PCA- Dose
  - Same as above / hourly dose (e.g. 0.4 mg morphine)
  - Unless there is a good reason not to...

PCA Order Set

- (3) Lockout time:
  - (5) - 10 minutes
- (4) Maximum number of boluses per hour:
  - 4 (-6) ....however, depends on the clinical scenario
- Loading dose? ...depends... (hourly dose x 1-4...)
- Lower starting dose? ...depends...age... if multimodal analgesia...
- How to increase the dose?
  - 50 per cent rule
Example for 50% titration orders:

- Patient (or nurse-) controlled analgesia: PCA
- Background infusion i.v./s.c.: 0.4 mg/hr
- Bolus i.v./s.c.: 0.4 mg (max 6 per hour); Lockout time: 5 (1-10) minutes

Example for 50% titration orders:

If receiving > _ boluses/hour for > _ consecutive hours AND if unrelieved pain AND no over sedation or dose limiting side effects, increase PCA by 50% as follows:

- Step 1: Continuous infusion 0.6 mg/hr, PCA dose 0.6 mg, max. 6 boluses/hr
- Step 2: (if ↑ again) Continuous infusion 0.9 mg/hr, PCA dose 0.9 mg, max. 6 boluses/hr
- Step 3: (if ↑ again) Continuous infusion 1.35 mg/hr, PCA dose 1.35 mg, max. 6 boluses/hr

Further Training

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer | Phoenix, AZ | May 4-5, 2015
http://www.cvent.com/d/q4qy0y

8th Annual Pediatric Pain Master Class | Minneapolis, MN | June 20-26, 2015 http://www.cvent.com/d/24q69s