Pharmacological Management of Pediatric Chronic Pain

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Learning Objectives

• By the end of this session, participants will be able to:

➢ To summarize the evidence regarding commonly used analgesics in children and adolescents.

➢ To outline analgesic indications for pediatric chronic pain.

➢ To review the use and limitations of analgesics for common types of chronic pain.
• Approximately how many Canadian children and adolescents experience chronic pain?

A. 1 in 2
B. 1 in 5
C. 1 in 10
D. 1 in 20
# Common causes of chronic pain in Children

<table>
<thead>
<tr>
<th>Pain Sites</th>
<th>Prevalence (Range)</th>
<th>Age differences</th>
<th>Sex Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8-82.9%</td>
<td>Older&gt;younger</td>
<td>Girls&gt;boys</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.8-53.4%</td>
<td>Younger&gt;older</td>
<td>Girls&gt;boys</td>
</tr>
<tr>
<td>Back Pain</td>
<td>13.5-24%</td>
<td>Older&gt;younger</td>
<td>Girls&gt;boys</td>
</tr>
<tr>
<td>Musculoskeletal/limb pain</td>
<td>3.9-40%</td>
<td>Older&gt;younger</td>
<td>Girls&gt;boys</td>
</tr>
<tr>
<td>Multiple pains</td>
<td>3.6-48.8%</td>
<td>Unclear</td>
<td>Girls&gt;boys</td>
</tr>
<tr>
<td>Other/general pain</td>
<td>5-88%</td>
<td>Unclear – possible age X sex interaction</td>
<td>Girls&gt;boys</td>
</tr>
</tbody>
</table>

(King et al., 2012)
IMPROVED PAIN SCALE

1. It might be an itch

2. I just need a bandaid

3. It's kind of annoying

4. This is concerning, but I can still work

5. Bees?

6. Bees!

7. I can't stop crying

8. I can't move, it hurts so bad

9. Mauled by a bear or ninjas

10. Unconscious
Types of Pain:

Nociceptive pain:
- Pain from actual or potential damage to non-neural tissue.

Neuropathic pain:
- Pain that arises from a lesion or disease of somatosensory nervous system.

Nociplastic pain:
- Pain from a dysfunction of the nervous system.
How to classify chronic pain?

Pain

- Nociceptive
  - Normal stimulation of nociceptors
    - Somatic
    - Visceral

- Neuropathic
  - Abnormal nervous system activation
    - Central
    - Peripheral
Neuropathic Pain Prevalence:

- Prevalence of neuropathic pain in adults is estimated to range from 1-8% in the general population.
- Prevalence of neuropathic pain in children is unknown.
- Some of the common neuropathic pain conditions seen in adults are rare in children.
- In comparison to nociceptive pain, neuropathic pain is:
  - Often more debilitating.
  - More difficult to diagnose and treat.
  - More impact on overall quality of life.
Central Sensitization:

- Previous inputs which were below threshold now reach threshold and initiate action potential.
  - Stimuli that generally do not provoke pain can produce pain (allodynia).
  - Stimuli that normally provoke pain can produce pain of a higher intensity (hyperalgesia).
- Increase in spontaneous activity.
- Enlargement of the area in periphery where stimulus will activate neurons.
In your clinical practice, do you typically prescribe or recommend pain medications to children and adolescents?

- A) Yes
- B) No
Pharmacotherapy For Chronic Pain:

Tired               Sad                Achy         Can’t sleep       Anxious         Scared          Stressed
Zoom Poll Question

• When treating a child’s chronic pain, which of the following is true.

A. Best treated with medication alone
B. Usually responds to one modality
C. Psychological strategies are not effective if they have neuropathic pain
D. Multidisciplinary and multimodal approach is the most effective in treating chronic pain.
The Perfect Analgesic

- Highly effective
- Safe with no side effects:
  - No sedation or respiratory depression
  - No constipation
  - No nausea
  - No withdrawal, dependence, tolerance, addiction.
- Easy to administer
- No drug interactions
- Cheap
- Quick onset, acceptable duration of action
Biopsychosocial Model

Environmental Factors
- Family
- School
- Peers

Psychological Factors
- Temperament
- Anxiety & Mood
- Coping Style
- Family and child beliefs about pain

Child Factors
- Age
- Gender
- Cognitive Level

Level of Disability
- Sleep
- School
- Social
- Physical

Physiological
- General Health
- Pain Characteristics
- Hormone Levels
- Injury
Multidisciplinary Pediatric Pain Treatment:

**Pharmacological**
- WHO ladder
- Adjuvant tx

**Physical**
- Ice/heat
- Positioning
- TENS
- Massage

**Psychological**
- Education
- Distraction
- Relaxation

PATIENT
Patient Brad:

- 15 y boy with h/o thoracic outlet syndrome requiring surgery x 2 one year ago.
- h/o depression and anxiety prior to surgery, managed with fluoxetine.
- After surgery, he developed deep throbbing shoulder pain and shooting pain that starts in his shoulder and runs down his arm to his fingertip multiple times daily.
- Function: disrupted sleep, unable to focus at school, stopped playing basketball.
- Developed suicidal ideations.
Multimodal Treatment Plan:

- **Pain**
  - Opioids
  - $\alpha_2$-Agonists
  - Centrally acting analgesics (acetaminophen)
  - Anti-inflammatory agents

- **Trauma**
  - Local anesthetics
  - Opioids
  - $\alpha_2$-Agonists
  - NMDA antagonists

- Local anesthetics
- Anti-inflammatory agents
- COX-2 inhibitor
- Ice
Pharmacological Treatment of Pediatric Pain

• There’s very little evidence and guidelines to support medication use in pediatric population. Often rely on extrapolating adult data and expert consensus.
• Pediatric analgesic trials are difficult to conduct.
• Most medications are used off-label
• Reinforce with patient and family that medication is just one part of a multi-prong attack.
WHO Analgesic Ladder – Cont.

- Oral dosing whenever possible.
- Around the clock administration rather than on-demand.
- Prescribe analgesics according to pain intensity.
- Individualized therapy addressing the concerns of the patient.
Pediatric Analgesic Pharmacokinetics

- **Newborn to toddlers:**
  - Delayed maturation of liver drug metabolizing enzymes compared to older children and adults until approximately 6 months of age.
  - Slower kidney glomerular filtration rate (GFR) until two years of age.
  - Delayed drug metabolism and clearance
  - Maturing respiratory drive – careful opioid titration and monitoring

- **School aged children**
  - Often higher weight based dosing, rapid clearance of drugs

- **Adolescents:**
  - similar to adults
Pharmacological Treatments

Acute Pain Treatments:
• Acetaminophen
• NSAIDs
• Opioids (short term)
• Muscle relaxant (for acute muscle spasms)
• Topical treatments

Chronic Pain Treatments
• Acetaminophen
• NSAIDS
• Anticonvulsants
• Antidepressants
• Topical Medications
• Opioids (in some cases)
• Nerve blocks
Simple Analgesics:

- **Step 1**: Pain
  - Non-opioid analgesic ± adjuvant

- **Step 2**: Persistent or increasing pain
  - Weak opioid ± non-opioid ± adjuvant

- **Step 3**: Persistent or increasing pain
  - Strong opioid ± non-opioid ± adjuvant
Acetaminophen

- Most widely used analgesic in children.
- It is safe in all age groups and has a low side effect profile.
- Good for mild to moderate pain by itself.
- Lack anti-inflammatory effects.
- Potentiated effect when combined with other analgesics such as NSAIDS or opioids.
- Keep an eye on maximum dose – particularly when patients are taking other acetaminophen combination products.

• Neonates and infants undergoing major thoracic or abdominal surgery were randomized to iv paracetamol vs continuous morphine group.
• The paracetamol group received 66% less cumulative morphine in the first 48 hours postoperatively compared to morphine group.
• Pain scores and adverse events were not significantly different between groups.
Nonsteroidal Anti-inflammatory Drugs

- NSAIDS provide pain relief, decrease inflammation, and reduce fever through direct inhibition of prostaglandin synthesis via the cyclooxygenase (COX) pathway.
- Risks include GI and renal toxicity with chronic use, especially in children with associated risk factors.
- Ibuprofen is the most commonly used NSAID in children 6 months of age or older.
- First line treatment for: musculoskeletal pain, inflammatory arthritis, dysmenorrhea, and abortive treatment for acute migraines.
- Acetaminophen and NSAIDS can be safely combined without an increase in their adverse effects.
NSAIDS Selectivity:

- Keterolac
- Indomethacin
- Naproxen
- Ibuprofen
- Diclofenac
- Celecoxib

Log [IC₈₀ ratio (COX-2/COX-1)]
Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial

Poonai N et al. CMAJ 2014

• Morphine vs Ibuprofen RCT
• 134 children with uncomplicated extremity fractures were randomized to receive either morphine (0.5 mg/kg) or ibuprofen (10 mg/kg) for 24 hours after discharge.
• No difference in pain scores at any time point.
• Less nausea with ibuprofen (NNT=5)
## Non-Opioids for Mild Pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Interval</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>10-15 mg/kg</td>
<td>4-6 h</td>
<td>Many oral dosage forms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>160mg/5ml liquid</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>5-10 mg/kg</td>
<td>6-8 h</td>
<td>10 mg/1ml; 200mg, 400mg, 600mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>5 mg/kg</td>
<td>12 h</td>
<td>125 mg/5ml; 220, 250 mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1 mg/kg</td>
<td>8-12 h</td>
<td>25 mg, 50 mg</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1-2 mg/kg</td>
<td>12-24 h</td>
<td>100, 200 mg</td>
</tr>
</tbody>
</table>
Adjuvant Analgesics:
Neuropathic Pain Treatments

- Gabapentinoids
- TCA
- SNRIs
- Opioid analgesics
- Cannabinoids
- Topical Lidocaine, Methadone
### 1st Line: Gabapentin and Pregabalin

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Potent anticonvulsant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Bind to presynaptic voltage gated calcium channel, Unclear mechanism</td>
</tr>
</tbody>
</table>
| **Elimination**  | Renal clearance  
Dosage must be adjusted proportional to reduction in creatinine clearance.  
No liver metabolism  
No known drug interaction |
| **Side Effects**  | Somnolence, dizziness, ataxia, nystagmus, tremor, disinhibition and rage |
Gabapentinoids

- **Pregabalin:**
  - Pregabalin in juvenile fibromyalgia: failed to show analgesic benefit compared to placebo, although secondary outcome measures including global impression of change were significantly improved in the treatment group.
  - Start at 0.5-1mg/kg BID and titrate up to 2 mg/kg BID.

- **Gabapentin:**
  - Available in liquid formulation
  - Easier titration, particularly in younger children
  - Start low, go slow.
  - Start at 2 mg/kg TID, titrate slowly up to 10 mg/kg TID
**1st Line: Amitriptyline, Nortriptyline**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Tricyclic Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Inhibit reuptake of serotonin and norepinephrine</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Metabolized by CYP450 2D6</td>
</tr>
<tr>
<td></td>
<td>Variation in metabolism due to genetic polymorphism</td>
</tr>
<tr>
<td></td>
<td>potential for drug interactions and serotonin syndrome e.g. tramadol, SSRI</td>
</tr>
<tr>
<td></td>
<td>Risk of QT prolongation and drug interaction (eg. Ondansetron, methadone, erythromycin)</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Dry mouth, Dizziness, somnolence, postural hypotension, disinhibition, blurred vision, ataxia</td>
</tr>
</tbody>
</table>
Clinical pain research

A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children

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HIGHLIGHTS

• 1st paediatric study for amitriptyline and gabapentin for CRPS I and neuropathic pain.
• Amitriptyline and gabapentin proved similarly effective for decreasing pain scores.
• No difference between amitriptyline and gabapentin in decreasing sleep disruption.
• No difference between amitriptyline and gabapentin in adverse events.
### **1st Line: Duloxetine, Venlafaxine**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>SNRI - Duloxetine, Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Selective serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Metabolized by CYP450 – potential for drug interactions and serotonin syndrome</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Sedation, fatigue, diarrhea, constipation, nausea, insomnia, hypersomnia, dizziness, weakness, drowsiness, headaches, agitation, vomiting, tension, nervousness 2-fold increase in suicidal ideation and behavior in children and adolescents</td>
</tr>
</tbody>
</table>
184 adolescents with juvenile fibromyalgia randomized to duloxetine or placebo for 13 weeks.

No significant difference in average pain intensity.

More patients taking duloxetine had a treatment response (> 30% and > 50% reduction in average pain intensity) and improvement of general activity and relationship with others items on the BPI.
**Cannabinoids:**


<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Pain Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study (Canada)</td>
<td>Retrospective cohort study</td>
<td>28 children aged 4 to 16 with chronic noncancer pain</td>
<td>Nabilone 0.25–4 mg/day for variable duration</td>
<td>25% of patients reported a small reduction of between 0.5 and 1.5 on the Numeric Rating Scale in pain scores</td>
</tr>
<tr>
<td>Libzon et al.\textsuperscript{12} (Israel)</td>
<td>Randomized noncontrolled trial (no placebo control group)</td>
<td>25 Children aged 1 to 17 years with complex motor disorders</td>
<td>Patients were randomized to two different CBD-enriched 5% oil formulations (CBD-to-THC ratio 6:1 vs. CBD-to-THC ratio 20:1) administered for 5 months</td>
<td>1.41-point reduction in pain out of 10 on visual analog scale in both treatment groups</td>
</tr>
<tr>
<td>Rudich et al.\textsuperscript{11} (Canada)</td>
<td>Case report</td>
<td>Two adolescents with CRPS type 1</td>
<td>Dronabinol 5–25 mg/day for 4 months</td>
<td>One participant reported 45% improvement in pain intensity, whereas the second reported no improvement; 50% reduction in affective component of their pain</td>
</tr>
</tbody>
</table>

*Table 4: Summary of previous studies on the use of cannabinoids for chronic noncancer pain treatment in children and adolescents.*
Cannabis Exposure and Brain Development in Youth

- **Structural Changes on MRI**
  - Lower brain volumes
  - Different folding patterns
  - Thinning of the cortex
  - Less neural connectivity
  - Lower white matter integrity

- **Functional MRI**
  - Demonstrated increased neural activity – brain is working harder to perform task.

- **Increased risk of developing mental health issues (depression, suicidal behavior).**
Cannabinoids Guideline:

- There are some evidence from studies in adults that suggest cannabinoids may have a place in treating chronic pain, but there is little research to directly support the use of cannabinoids to treat pediatric chronic pain.
- Recommend using evidence informed clinical judgement to weigh the potential benefits and harms on a case-by-case basis.
Opioids:

Step 1: Non-opioid analgesic ± adjuvant

Step 2: Weak opioid ± non-opioid ± adjuvant

Step 3: Strong opioid ± non-opioid ± adjuvant

Persistent or increasing pain
• Health Canada recommendations:
  • Codeine should not be used in patients under 18 years to treat pain after surgery to remove tonsils or adenoids.
  • It is not recommended for children under age 12 for any use.
• FDA
  • Tramadol should not be used in children younger than 18 years after T and A surgery and in adolescents who are obese or have conditions such as OSA or severe lung disease.
Opioids

- **Morphine:**
  - Avoid in children with renal failure
  - Can be given in oral, IV, and IM routes

- **Hydromorphone:**
  - Less pruritus than morphine

- **Oxycodone:**
  - Undergoes partial metabolism by CYP2D6 to an active metabolite. Pharmacokinetics is also variable, especially in infants

- **Tramadol:**
  - Weak agonist at the Mu opioid receptor and weak inhibitor of norepinephrine and serotonin reuptake.
  - Also has metabolism by CYP2D6 enzyme
  - FDA does not recommend tramadol use in children.
Low Dose Naltrexone (LDN)

- Opioid antagonist
- Proposed mechanism:
  - Briefly blocking opioid receptors up-regulates endogenous endorphins.
  - Down regulates inflammatory cytokine release
- Low dose – 0.5 – 4.5 mg once daily.
- Small clinical trials suggest some efficacy in Crohn’s disease and Fibromyalgia.
If a child develops pruritus with morphine, all opioids should be avoided for pain treatment in the future.

A) True
B) False
### Common Opioid Related Side Effects

<table>
<thead>
<tr>
<th>Pruritus:</th>
<th>Emesis:</th>
<th>Sedation:</th>
<th>Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anti-pruritic: cetirizine</td>
<td>• PRN anti-emetics</td>
<td>• Decrease opioid dose if pain well managed</td>
<td>• Decrease opioid dose if pain well managed</td>
</tr>
<tr>
<td>• Low dose naloxone: 0.25 - 1 mcg/kg/h</td>
<td>• Optimize opioid sparing analgesics</td>
<td>• Rotate opioid</td>
<td>• Promote physical activity</td>
</tr>
<tr>
<td>• Rotate opioid</td>
<td>• Rotate opioid</td>
<td>• Switch to enteral route in patient tolerates</td>
<td>• Stool softener, laxatives</td>
</tr>
</tbody>
</table>
Opioids have a crucial role in the treatment of moderate to severe pain in children and adolescents.

**Dose:**
- Prescribe the lowest estimate effective dose and allow for upward titration if analgesia is ineffective. (low and slow)
- Prescribe short-acting opioids for acute pain.

**Duration:**
- Prescribe no more than what is needed for the expected duration of moderate to severe pain.

**Education:**
- Provide education on expectation regarding pain, how the efficacy of opioids will be assessed, and tapering of medication.
- Instruct patient and families on safe storage and disposal of leftover opioids to minimize the risk of diversion and accidental ingestion.
How should we instruct families to dispose of unused prescription opioids in the home?

A. Flush down the toilet
B. Dispose in trash can
C. Return to local pharmacy
D. Keep in medicine cabinet in case they need it in the future.
Opioid Prescribing for Chronic Pain

• No guidelines available to guide decision making.
• Which pediatric chronic non-cancer pain conditions?
  • Tissue damage – e.g. severe inflammatory MSK pain, EB.
  • Severe CRPS to facilitate PT
  • Sickle Cell disease, Osteogenesis Imperfecta, Ehler Danlos.
• Opioids do not have a role in the majority of primary pain conditions in children including abdominal pain, headache, and widespread MSK pain.
• Emphasize improvement in function
  • Only use if there is clear evidence of improved function
  • Always have a specific functional objective in mind; otherwise it’s stopped.
Goal Setting

- Set realistic expectations.
- The focus is not complete elimination of pain.
- With chronic pain, focus more on function and less on a pain scale.
- Only use if there is clear evidence of improved function.
- Re-evaluate impact on function frequently.

“I want to be able to go on a 30 minute bike ride with my friends by the end of summer”
Canada's First National Pediatric Pain Management Standard.
Pediatric Pain National Standard

• Opioids can be used as a co-therapy for managing moderate-severe pain in children

• Acute Pain
  • Use the lowest effect dose of the most appropriate opioid for the shortest duration necessary for managing the child’s pain.
  • Typically a duration of three days or less is required for uncomplicated procedures or injuries.

• Chronic Pain:
  • If there is a need for long-term opioid use, establish a clear plan that identifies a single prescriber and include regular follow up, communication, and record keeping.
American Pain Society: Assessment and Management of Children with Chronic Pain

➢ Opioids are rarely indicated in the long-term treatment of chronic nonmalignant pain in children, although they may be beneficial in certain painful conditions with clearly defined etiologies (e.g., sickle cell disease, incurable degenerative joint and neurodegenerative diseases, etc.).

➢ Consultation or referral to a pediatric chronic pain specialist should be strongly considered in these cases.
What percentage of adolescents in Ontario report using a prescription opioid analgesic without medical prescription in the past year?

A. 1%
B. 2%
C. 5%
D. 10%
E. 20%
Past Year Nonmedical Use of Prescription Opioid Pain Relievers in Ontario
Non-medical use of Prescription Opioids in adolescents

• Through unused prescriptions, healthcare providers may inadvertently add to the supply of opioids within the community.
• Among high school seniors who report non-medical use of prescription opioids, 80% access leftover medication from a legitimate prescription.

Note: The percentages do not add to 100 percent due to rounding.
GENERAL PRINCIPLES OF CHRONIC PAIN MANAGEMENT

• Balanced Analgesia - More than one class of analgesic or adjuvant each working in a different way = better pain relief with fewer side effects
• Start low and go slow – titration is critical to limiting side effects
• Trial and error approach – inter-individual variation in response to treatment.
• Set realistic expectations: improve function with minimal side effects, and reduce pain.
Multidisciplinary Pediatric Pain Treatment:

Pharmacological
- WHO ladder
- Adjuvant tx

Physical
- Ice/heat
- Positioning
- TENS
- Massage

Psychological
- Education
- Distraction
- Relaxation
Patient Brad:

- Trialed Gabapentin, Pregabalin, Amitriptyline, Nabilone and Compound topical pain medication.
- Venlafaxine found to be most helpful.
- PT: desensitization exercises, graded exercise program.
- Psychology to help manage mood and anxiety - mindfulness, acceptance commitment therapy.
- OT: school liaison to help advocate for accommodation.
- Continued to struggle with chronic pain, but pain and function both slowly improving.
- His mood also improved and no longer considering self harm.
Key Take-away Messages

• Analgesics have useful roles for many kinds of pain.
• Pharmacological treatment is just one prong of the multi-disciplinary pain treatment.
• Opioid prescribing is indicated for acute pain, cancer pain, sickle cell pain, and for end of life symptoms.
• Chronic opioid prescribing should be used with great caution for chronic non-cancer pain.
• Long-term medications should be used with caution and with consideration of risks, benefits and alternatives.
• Emphasize improvement in function.
References:


Questions?

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