Pharmacological Management of Pediatric Chronic Pain

Naiyi Sun, MD Staff Anesthesiologist, The Hospital for Sick Children Assistant Professor, University of Toronto

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Faculty/Presenter Disclosure

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 - None
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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.

Zoom Poll Question

- 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

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





))) 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?



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.



Zoom Poll Question

- In your clinical practice, do you typical prescribe or recommend pain medications to children and adolescents?
 - A) Yes
 - B) No

Pharmacotherapy For Chronic Pain:



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



Multidisciplinary Pediatric Pain Treatment:





PATIENT

Physical

- Ice/heat
- Positioning
- TENS
- Massage

Psychological

- Education
- Distraction
- Relaxation





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:



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.



Mapted WHO Analgesic Ladder



WHO Analgesic Ladder – Cont.

Oral dosing whenever possible.

Around the clock administration rather than ondemand.

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:



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.



Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery A Randomized Controlled Trial

- Ceelie et al. JAMA 2013; 309 (2):149-154.
 - 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:





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

Medication	Initial Dose	Interval	Dosage Forms
Acetaminophen	10-15 mg/kg	4-6 h	Many oral dosage forms 160mg/5ml liquid
Ibuprofen	5-10 mg/kg	6-8 h	10 mg/1ml; 200mg, 400mg, 600mg
Naproxen	5 mg/kg	12 h	125 mg/5ml; 220, 250 mg
Diclofenac	1 mg/kg	8-12 h	25 mg, 50 mg
Celecoxib	1-2 mg/kg	12-24 h	100, 200 mg

Adjuvant Analgesics:







))) 1st Line: Gabapentin and Pregabalin

Drug Class	Potent anticonvulsant
Mechanism of Action	Bind to presynaptic voltage gated calcium channel, Unclear mechanism
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

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





Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com



Clinical pain research

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

S.C. Brown^{a,b,*}, B.C. Johnston^{a,b,c,d}, K. Amaria^e, J. Watkins^{a,b}, F. Campbell^{a,b}, C. Pehora^a, P.A. McGrath^f

^a Department of Anesthesia and Pain Medicine, Hospital for Sick Children, Toronto, Ontario, Canada

^b University of Toronto, Toronto, Ontario, Canada

- ^c Child Health Evaluative Services, The Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada
- ^d Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
- e Department of Psychology, The Hospital for Sick Children, Toronto, Ontario, Canada

f Pain Innovations Inc., London, Ontario, Canada

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

Drug Class	SNRI - Duloxetine, Venlafaxine
Mechanism of Action	Selective serotonin and norepinephrine reuptake inhibitor
Drug Interactions	Metabolized by CYP450 – potential for drug interactions and serotonin syndrome
Side Effects	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



Research article Open Access Published: 28 May 2019

Efficacy and safety of duloxetine versus placebo in adolescents with juvenile fibromyalgia: results from a randomized controlled trial

Himanshu P. Upadhyaya 🖂, Lesley M. Arnold, Karla Alaka, Meihua Qiao, David Williams & Renata Mehta

<u>Pediatric Rheumatology</u> **17**, Article number: 27 (2019) <u>Cite this article</u>

- 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:

Study		Patient		
(country)	Study Design	Characteristics	Intervention	Pain Outcomes
Current study (Canada)	Retrospective cohort study	28 children aged 4 to 16 with chronic noncancer pain	Nabilone 0.25–4 mg/day for variable duration	25% of patients reported a small reduction of between 0.5 and 1.5 on the Numeric Rating Scale in pain scores
Libzon et al. ¹² (Israel)	Randomized noncontrolled trial (no placebo control group)	25 Children aged 1 to 17 years with complex motor disorders	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	1.41-point reduction in pain out of 10 on visual analog scale in both treatment groups
Rudich et al. ¹¹ (Canada)	Case report	Two adolescents with CRPS type 1	Dronabinol 5–25 mg/day for 4 months	One participant reported 45% improvement in pain intensity, whereas the second reported no improvement; 50% reduction in affective component of their pain

Sun N et al. Synthetic cannabinoids for the treatment of severe chronic noncancer pain in children and adolescents. Can J Pain. 2022

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:







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Codeine: Time to Say "No"

Joseph D. Tobias, MD, Thomas P. Green, MD, Charles J. Coté, MD, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE, COMMITTEE ON DRUGS

- 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.

Zoom Poll Question

- 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

Pruritus:	Emesis:	Sedation:	Constipation
 Anti-pruritic: cetirizine Low dose naloxone: 0.25 - 1 mcg/kg/h Rotate opioid 	 PRN anti- emetics Optimize opioid sparing analgesics Rotate opioid Low dose naloxone 	 Decrease opioid dose if pain well managed Rotate opioid Switch to enteral route in patient tolerates 	 Decrease opioid dose if pain well managed Promote physical activity Stool softener, laxatives

Opioids Prescribing for Acute Pain

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.

Zoom Poll Question

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.

CAN/HSO 13200:2023 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.

Zoom Poll Question

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 nonmedical use of prescription opioids, 80% access leftover medication from a legitimate prescription.



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:



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 accomodation
- 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 multidisciplinary pain treatment.
- Opioid prescribing is indicated for acute pain, cancer pain, sickle cell pain, and for end of life symptoms.

Important Nessage

- 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.

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Questions?





naiyi.sun@sickkids.ca

