



DRUG PROGRAMS Prescription Review Program Opioid Agonist Therapy Program 101 - 2174 Airport Drive Saskatoon, SK S7L 6M6 prp@cps.sk.ca oatp@cps.sk.ca cps.sk.ca Business: (306) 244-7355 Fax: (306) 912-8944 Toll Free: (800) 667-1668

INFORMATIONAL

May 30, 2025

RE: Tramadol use in pediatrics

Dear Dental colleague,

The *Prescription Review Program* (PRP) is Saskatchewan's educationally focused prescription monitoring program administered by the **College of Physicians and Surgeons of Saskatchewan**.

Health Canada conducted a safety review of tramadol in children and adolescents as a follow-up to their study on codeine and the risk of serious breathing problems in children¹. As a result of the safety evaluation, Health Canada updated tramadol's product information to highlight the risk of serious breathing problems associated with its use, similarly to codeine². Tramadol is often thought to be a safer alternative to codeine or other oral opioids in pediatrics, which may stem from the familiarity of its use in the adult population, association with lower rates of certain opiate-related adverse effects such as constipation, and belief that is causes less risk of respiratory depression¹. Following Health Canada's safety review, and increased concerns in the medical community regarding its use in pediatric patients^{3,15}, we have conducted our own analysis on tramadol prescribing trends in Saskatchewan for patients under the age of 18.

Tramadol is an analog of codeine that appears to exert its analgesic effects though being both a weak agonist at the μ -opiate receptor and a weak inhibitor of norepinephrine and serotonin reuptake¹. Like codeine, tramadol is also metabolized by cytochrome P450 liver enzymes, primarily CYP2D6 and CYP3A4. The active metabolite produced through the CYP2D6 metabolic pathway (O-desmethyltramadol) has much greater affinity for the μ receptor than tramadol itself¹. The metabolism of tramadol is dependent on the CYP2D6 phenotype of the individual, which is highly more variable and unpredictable in children compared to adults³. This results in:

- Poor metabolizers: may be underdosed and have poor pain management³
- Ultrarapid metabolizers: may be at increased risk of toxicity and respiratory depression from more rapid conversion to O-desmethyltramadol³

It is always important to treat pain as a multimodal approach, combining physical, psychological and pharmacologic interventions to establish the best pain management treatment plan for each individual¹⁶. Multimodal analgesia for acute pain is most effective for pediatric pain management, preventing transition from acute to chronic pain⁴. For chronic pediatric pain, a multidisciplinary approach is recommended (e.g. physical therapy; occupational therapy; psychological intervention; "normalizing" life with school, sleep, and social activities; etc.)⁴ with non-opioid medications and counselling, infrequently requiring opioid use¹⁷.

Canadian Pediatric Society (CPS) Pain Management Guidelines and Protocols¹⁴

Analgesics for pain should be used in a stepwise manner, combined with physical and psychological strategies.

- **Step 1** (mild to moderate pain): ibuprofen; acetaminophen can be used 1st line for mild pain if ibuprofen is contraindicated;
- **Step 2** (moderate to severe pain): morphine[±] is the medicine of choice (acetaminophen +/- ibuprofen used as co-analgesia)
 - Patients presenting with acute moderate to severe pain unlikely to be resolved by physical and psychological strategies and first line analgesics should be offered pharmacological interventions on an escalating basis. Opioids should be used judiciously, with appropriate dosing assessment to avoid adverse events and careful monitoring.
- Dose at regular intervals, while monitoring side-effects.
- Consider the appropriate route of administration (e.g. IM can be painful with erratic absorption; rectal can have unreliable bioavailability).
- Adapt treatment to the individual child.

Therapeutic Options⁶

Abdominal (acute)	-use of opioids* does not delay surgical decision (relaxed patient may provide better
	exam and better diagnosis)
Minor Burns	-Cold compress
	-Ibuprofen or acetaminophen
Earache	-Warm cloth
	-Ibuprofen or acetaminophen (initiate quickly)
	-Auralgan (antipyrine & benzocaine) – avoid with perforated ear drum
Emergency Trauma	-Musculoskeletal: ibuprofen (superior to acetaminophen or codeine)
	-Opioids* (e.g. morphine [±]) if moderate to severe pain**
	- Cold compresses *e.g. for sprains), splinting, elevation, bandaging +/- dressing
Heel Poke	-Breastfeeding, sucrose, sucking
Immunization	-Pressure at site
	-Sucrose (infants up to 12 months of age)
	-Topical anesthetics
Open wound	-Topical anesthetic (e.g. LET, lidocaine 4%/epinephrine 0.1%/tetracaine 0.5%) – avoid
(foreign body ruled	mucous membranes; avoid epinephrine on digits, nose tip, ear, penis
out)	-Tissue adhesive
Post On (analgosia)	NSAID - acataminanhan
Post-Op (analgesia)	-NSAID + acetaminophen may add aniaid* DDN for 2. E days for sovere pain (soution adopt, tonsillactomy)
	sold (warm compress
	-start analgesia before child wakes up (e.g. suppository)

*Appropriate monitoring for respiratory depression, sedation and reduced consciousness is essential⁷

[±]For acute/persisting pain treatment, if an opioid is indicated, morphine is preferred over tramadol or codeine because of the CYP 2D6 polymorphisms and risk of respiratory depression. Although there is less evidence compared to codeine, there are case reports describing incidences of tramadol overdoses⁸

**In an RCT of children presenting to the ED with an <u>uncomplicated</u> extremity fracture, children received oral morphine (0.5mg/kg) or ibuprofen for 24 hours after discharge. No significant difference in analgesic efficacy was noted between oral morphine and ibuprofen; morphine was associated with significantly higher adverse effect⁹.







<u>·····································</u>				
Drug	Application	Caution		
Emla	60+ min prior with occlusion	-Vasoconstriction		
(lidocaine + prilocaine)		-Rare risk of methemoglobinemia		
Ametop (tetracaine gel)	30-45 min with occlusion	-Vasodilation		
		-Must refrigerate		
Maxilene	15-45+ min prior	-Minimally vasoactive		
(Liposomal Lidocaine)				

Topical Anesthetics (for Intact Skin, avoid middle ear)⁶

Topical analgesics may also be considered for chronic pain⁷.

General Non-Pharmacological Suggestions (as age appropriate)^{6,7,17}

- Affirmative language
- Parental counselling parental anxiety in the context of children undergoing acute procedural pain is one of the most powerful predictors of pain outcomes¹⁵
- Consider psychology/psychiatry consult if necessary
- Physical comfort strategies (e.g. kangaroo care, comfort positioning, facilitated tucking or touch)
- Distraction (books, bubbles, TV, breathing, breastfeeding, music, virtual reality, conversation)
- Techniques to reduce stimulation (e.g. minimizing harsh lighting and/or noise)¹⁷
- Hot/cold compresses (not for neonates)
- Warm blanket
- Massage
- Activity out of bed
- Elevation
- Splinting, bandaging, dressing
- Injury site pressure

Non-Opioid Oral Analgesic Therapies and Dosing¹⁸

Drug	Dosing	Max Daily Dose	
Acetaminophen [#]	10-15 mg/kg/dose every 4-6	75 mg/kg/day (maximum of	
	hours	1000mg/dose)	
		Newborn (4-40 wks.): 60 mg/kg/day	
Ibuprofen [#]	5-10 mg/kg/dose every 6-8	40 mg/kg/day (maximum of	
	hours	600mg/dose)	
Naproxen	>2years old-5-7 mg/kg every 8-	20 mg/kg/day (maximum of	
	12 hours	500mg/dose)	
Antidepressants (e.g. TCAs), anticonvulsants (e.g. gabapentin), SNRI's (e.g. duloxetine)			

[#]Consider initiating opioid-sparing analgesics (with side-effect monitoring) using upper doses to get the pain under control.

Ibuprofen provides more effective pain control in children compared to acetaminophen, particularly for acute pain, musculoskeletal trauma, headache, and post-dental extraction¹⁴.







If pain control with one form of non-opioid monotherapy is insufficient, switching is an alternative or combining acetaminophen + NSAID may be used short-term (noting the different dosing frequency is important). Caution is advised with alternating between acetaminophen and an NSAID because of the increased risk of adverse effects and potential errors. If a combination is used, advise caregiver to verify each dose and write down time of each administration to keep track¹⁸. In pain associated with dental extraction or tonsillectomy, the combination of acetaminophen and ibuprofen appears to be more effective than acetaminophen on its own¹⁴. Post-operative pain should be dosed as scheduled ("around the clock") and pre-ambulation or pre-procedure (excluding vaccination) analgesics are usually dosed PRN⁷.

Acetaminophen and NSAIDs may have a "ceiling effect" meaning that escalations above the recommended daily maximum analgesic dose are unlikely beneficial and may put the patient at a higher risk of adverse effects⁷.

As a reminder, if adequate non-opioid measures are ineffective and an opioid is indicated based on clinical judgment, it is strongly recommended that for acute pain and as initial therapy for chronic pain, the opioid prescription duration should not exceed 5-10 doses or 2-3 days¹⁷ (with back-up analgesia for beyond three days and plans for follow-up, as necessary) at the lowest effective dose alongside appropriate patient/parent/caregiver counselling for use, risk, management of adverse effects (including overdose), storage and potential for misuse¹⁰. One study showed that 14% of parents gave zero doses of prescription opioids to their children and 79% had leftovers after day three post-procedure; as such, discussion around proper disposal is also essential¹¹. It is recommended that acetaminophen and opioids are prescribed individually (i.e. not combination products such as acetaminophen with codeine) so that acetaminophen can be administered regularly, and the opioid can be used for breakthrough pain¹².

If opioids are used, they should be given alongside non-opioid analgesics to ensure that only the lowest dose of opioids is used¹⁶. We recognize that tramadol or codeine are often prescribed to give the lowest opioid dose possible. There is a 1mg/ml morphine oral liquid commercially available for lower dosing of morphine (e.g. 4.5mg of morphine is the approximate amount of codeine in a Tylenol #3 tablet).

The Canadian Pediatric Society issued a position statement¹³ in March 2021 entitled *The use of oral opioids to control children's pain in the post-codeine era* which provides five recommendations for practice to safely manage pediatric pain:

- Effective and safe pain control should be a focus of treatment plans for children with acute or chronic conditions, based on best practice guidelines and current evidence.
- Pain control should involve both pharmacologic and nonpharmacologic approaches and be appropriate for the case, setting, and nature of the pain.
- Medication choice and administrations should be both commensurate with the nature and severity of the pain and demonstrated to be effective and safe for use in children. Analgesics should be used in a stepwise manner, beginning with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) before progressing to opioids.
- While there are a number of oral opioid formulations available for analgesia for children, oral morphine is still the drug with the strongest evidence base for efficacy and safety. Other oral opioids appear promising, but more evidence is needed to establish their efficacy, safety, and role in therapy before using them routinely.









• Research into pain management for children in both acute and chronic settings is urgently needed.

Pediatric pain matters and needs to be treated safely and effectively. This correspondence is provided in hopes of assisting with the management of pediatric pain, incorporating some of the current evidence and resources on the topic.

Sincerely,

Prescription Review Program

College of Physicians and Surgeons of Saskatchewan Phone: 306-244-7355 Fax: 306-912-8944







Excellent Resources:

- Solutions for Kids in Pain (SKIP): <u>https://www.kidsinpain.ca/</u>
- Commitment to Comfort: <u>https://childkindinternational.org/wp-content/uploads/Commitment-to-Comfort-Parent-Guide.pdf</u>
- Best Practices in pain assessment and management for children (CPS): <u>https://cps.ca/en/documents/position/pain-assessment-and-management#ref21</u>
- Solutions for kids in pain (SKIP): Opioids and Pain in Youth: A toolkit for health professionals toolkit

References:

- 1. Canada H. Government of Canada [Internet]. Canada.ca. / Gouvernement du Canada; 2015 [cited 2022Dec2]. Available from:<u>https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-codeine-prescription-products-indicated-cough-further-assessing-risk-serious-breathing-problems-children-adolescents-1.html</u>
- 2. Canada H. Government of Canada [Internet]. Canada.ca. / Gouvernement du Canada; 2017 [cited 2022Dec2]. Available from:<u>https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-tramadol-potential-risk-serious-breathing-problems-children-adolescents.html</u>
- 3. Fortenberry M, Crowder J, So T-Y. The use of codeine and tramadol in the pediatric population—what is the verdict now? Journal of Pediatric Health Care. 2019;33(1):117–23.
- 4. Friedrichsdorf SJ, Goubert L. Pediatric pain treatment and prevention for hospitalized children. PAIN Rep, 2020;5(1): e804.
- 5. World Health Organization. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva: WHO Press, 2012.
- 6. Regier L, Jensen B, Kessler B, Wiebe A. Pediatric Pain: Treatment Considerations, Q&As. RxFiles 14th ed. Saskatoon, SK: RxFiles; 2023.
- 7. SHA Department of Pharmaceutical Services (RUH, SCH, SPH). Policies and Procedures: Pain Management Pediatric Care. Available from: https://www.saskatoonhealthregion.ca/about/NursingManual/1045.pdf
- 8. Rodieux F, Vutskits L, Posfay-Barbe KM, Habre W, Piguet V, Desmeules JA, et al. When the safe alternative is not that safe: Tramadol prescribing in children. Frontiers in Pharmacology. 2018;9.
- 9. Poonai N, et al. Oral administration of morphine versus ibuprofen to manage post fracture pain in children: a randomized trial. CMAJ, 2014;186(18): 1358-1363.
- 10. Matthews DC, et al. Patterns of opioid prescribing by dentists in a pediatric population: a retrospective observational study. CMAJO, 2019;7(3): E497-E503.
- 11. Voepel-Lewis T, Wagner D, Tait AR. Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. JAMA Pediatr, 2015;169: 497-8.
- 12. O'Donnell FT Rosen KR. Pediatric Pain Management: A Review. Mo Med, 2014;111(3): 231-237.
- 13. Rieder M, Jong G. Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee. The use of oral opioids to control children's pain in the post-codeine era. Paediatr Child Health, 2021; 26 (2): 120-123. Available from: https://cps.ca/documents/position/the-use-of-oral-opioids-to-control-childrens-pain-in-the-post-codeine-era
- Trottier ED, Dore-Bergeron M-J, Chauvin-Kimoff L. Best practices in pain assessment and management for children [Internet]. cps.ca. 2022 [cited 2022Dec2]. Available from: <u>https://cps.ca/en/documents/position/pain-assessment-and-management</u>
- 15. Gai N, Naser B, Hanley J, Peliowski A, Hayes J, Aoyama K. A practical guide to acute pain management in children. Journal of Anesthesia. 2020;34(3):421–33.
- 16. Solutions for Kids in Pain. Opioids and Pain in Youth: A toolkit for health professionals, 2023. Available from: https://www.kidsinpain.ca/youth-in-pain
- 17. Health Standards Organization (HSO). Pediatric Pain Management (Organizational Competency CAN/HSO 13200 :2023). Health Standards Organization (HSO), 2023. Available from: https://store.healthstandards.org/products/pediatric-pain-management-can-hso-13200-2023-e
- 18. Wiebe A, Regier L, Jensen B, Kessler B. Pediatric Pain: Drug Comparison Charts. RxFiles [Internet]. 2025 January. Available from: <u>https://www-rxfiles-ca.ezproxy.shirp.ca/RxFiles/uploads/documents/members/CHT-Pain-Peds.pdf</u>





