



Date

Dear Dental Colleague,

**RE: Codeine use in pediatrics**

The *Prescription Review Program* (PRP) is Saskatchewan's educationally focused prescription monitoring program administered by the College of Physicians and Surgeons of Saskatchewan on behalf of the Ministry of Health. One of our valued stakeholders is the College of Dental Surgeons of Saskatchewan.

Recently, we conducted an analysis to assess codeine prescribing for Saskatchewan patients under the age of 18 years in response to the updated Health Canada advisory warning that individuals under 18 years of age should not use non-prescription pain relief products containing codeine (previously not recommended for children under the age of 12 years)<sup>1</sup>. Health Canada provided an additional warning about the use of prescription cough and cold products containing opioids and the risk of opioid use disorder in children and adolescents (<18 years of age) as well as the risk of opioid toxicity<sup>10</sup>. Current literature suggests that early exposure to opioids in childhood and adolescence may put patients at risk for opioid-related adverse events throughout life<sup>2,6</sup>.

Historically, codeine was the preferred opioid analgesic in pediatrics, given the perception of safety and wide therapeutic index<sup>2</sup>. While there may be a lower incidence of CNS and respiratory depression after a single dose, the lower risk may not exist after subsequent doses<sup>9</sup>. As such, the thinking surrounding codeine safety changed around 2011 when the WHO noted that "efficacy and safety were questionable in an unpredictable portion of the pediatric population"<sup>2</sup>. Today, unless codeine has already been prescribed for a chronic condition, initiating treatment with codeine is not recommended.

Codeine, a prodrug with weak binding to the mu opioid receptor, has highly unpredictable metabolic properties, making it a risky therapeutic option for the pediatric population. The bioactivation to morphine provides the analgesic properties of codeine. Codeine is converted to morphine with the hepatic cytochrome P450 2D6 enzyme and analgesia is dependent on the individual's CYP2D6 gene. As a result, those with inactive CYP2D6 are "poor metabolizers" and will experience reduced pain relief as a result of the medication, given the reduced conversion to morphine. On the other hand, "ultra-rapid metabolizers" are at risk of overdose and adverse/toxic effects (which have resulted in pediatric deaths)<sup>13</sup>, even at lower doses, because of the rapid and complete metabolism to morphine<sup>3,4</sup>.

It has been estimated that anywhere from 77-92% of patients are considered “normal metabolizers”, suggesting expected enzyme activity and morphine formation; thus, “normal metabolizers” are candidates for dosing based on labeled recommendations<sup>3</sup>. Unfortunately, without genetic testing, gene variation is largely unknown in our general population.

An initial pain assessment is an important step for optimal pain management.<sup>17</sup> An appropriate assessment using a developmentally appropriate tool should include pain location, quality, duration and intensity.<sup>17</sup> Age appropriate assessments tools are available through [The Canadian Pediatric Society's](#) updated pain guidance.

It is always important to consider stepwise non-opioid and non-pharmacological options in pediatrics as first-line therapy. Multimodal analgesia for acute pain is most effective for pediatric pain management, preventing transition from acute to chronic pain<sup>13</sup>. 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.)<sup>13</sup>.

### **WHO Principles for Pharmacologic Management of Pain<sup>14</sup>**

Treatment of persisting pain due to medical illness relies on key concepts:

- Two-step strategy:
  - Step 1 (mild pain): acetaminophen and ibuprofen are the medicines of choice
  - Step 2 (moderate to severe pain): morphine<sup>±</sup> is the medicine of choice
    - *Bypassing Step 1 requires cautious clinical judgment (e.g. pain severity, consideration of disability caused by pain, cause of pain, expected prognosis, etc.)*
- 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

*<sup>±</sup>For acute/persisting pain treatment, if an opioid is indicated, morphine is usually preferred over codeine because of the CYP 2D6 polymorphisms and case-reports associated with overdose from codeine<sup>11,14</sup>*

### **General Non-Pharmacological Suggestions** (as age appropriate)<sup>5,8</sup>

Affirmative language

Parental counselling – parental anxiety in the context of children undergoing acute procedural pain is one of the most powerful predictors of pain outcomes<sup>15</sup>

Physical comfort strategies (e.g. kangaroo care, comfort positioning)

Distractions (e.g. books, bubbles, TV, breathing exercises, music, virtual reality, conversation)

Hot/cold compresses (not for neonates)

Activity out of bed

Dressings (with pressure, if appropriate)

### Oral Analgesic Therapies and Dosing<sup>5</sup>

Drug	Dosing	Max Daily Dose
Acetaminophen <sup>#</sup>	10-15 mg/kg/dose every 4-6 hours	75 mg/kg/day <sup>&gt;40wks</sup>
Ibuprofen <sup>#</sup>	5-10 mg/kg/dose every 6-8 hours	40 mg/kg/day
Naproxen	2.5-5 mg/kg BID	20 mg/kg/day

<sup>#</sup>Consider initiating opioid-sparing analgesics (with side-effect monitoring) using upper doses to get the pain under control.

Ibuprofen has been shown to be more effective than acetaminophen for children's pain, particularly for acute pain, musculoskeletal trauma, headache and post-dental extraction with a comparable safety profile.<sup>17</sup> Alternating between acetaminophen and a NSAID is not recommended because of the increased risk of adverse effects and potential for errors. Monotherapy is preferred, however, if insufficient, switching is an alternative or combining acetaminophen + NSAID may be used short-term (noting the different dosing frequency is important). For example, the combination of acetaminophen and ibuprofen to manage dental extraction or tonsillectomy pain is superior compared with acetaminophen alone.<sup>17</sup> Post-operative analgesics (e.g. acetaminophen, NSAIDs) should be dosed as scheduled ("around the clock") and pre-procedure analgesics are usually dosed PRN<sup>8</sup>.

Acetaminophen and NSAIDs may have a "ceiling effect" meaning that escalations above the recommended daily maximum dose are unlikely beneficial and may put the patient at a higher risk of adverse effects<sup>8</sup>.

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 3 days (with back-up analgesia for beyond 3 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 misuse<sup>2</sup>. One study showed that 14% of parents gave zero doses of prescription opioids to their children and 79% had leftovers after day 3 post-procedure; as such, discussion around proper disposal is also essential<sup>6</sup>. Acetaminophen and opioids should be 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 pain<sup>12</sup>.

The Canadian Pediatric Society issued a position statement in March 2021 entitled *The use of oral opioids to control children's pain in the post-codeine era*<sup>16</sup> which provides 5 recommendations for practice to safely manage pediatric pain:

1. 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.
2. Pain control should involve both pharmacologic and nonpharmacologic approaches and be appropriate for the case, setting, and nature of the pain.
3. 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.
4. 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.
5. 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)*: <https://www.kidsinpain.ca/>

*Commitment to Comfort*: <https://www.commitmenttocomfort.com/>

*Best Practices in pain assessment and management for children (CPS)*:

<https://cps.ca/en/documents/position/pain-assessment-and-management#ref21>

## References:

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