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Dear Nursing 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 partners is the Saskatchewan Registered Nurses Association.

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)[1]. 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[10]. Current literature suggests that early exposure to opioids in childhood and adolescence may put patients at risk for opioid-related adverse events throughout life[2,6].

Historically, codeine was the preferred opioid analgesic in pediatrics, given the perception of safety and wide therapeutic index[2]. 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[9]. 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"[2]. 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)[13], even at lower doses, because of the rapid and complete metabolism to morphine[3,4].

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[3]. Unfortunately, without genetic testing, gene variation is largely unknown in our general population.

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[13]. 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.)[13].

WHO Principles for Pharmacologic Management of Pain[14]

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$^{\pm}$ 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

Therapeutic Options[5]

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$^{\pm}$) if moderate to severe pain**
Heel Poke	-Breastfeeding, sucrose
Immunization	-Pressure at site -Sucrose (infants up to 12 months of age) -Topical anesthetics
Open wound (foreign body ruled out)	-Topical anesthetic (e.g. LET, lidocaine 4%/epinephrine 0.1%/tetracaine 0.5%) – avoid mucous membranes; avoid epinephrine on digits, nose tip, ear, penis -Tissue adhesive

**Appropriate monitoring for respiratory depression, sedation and reduced consciousness is essential*[8]
$^{\pm}$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[11,14]
***In an RCT of children presenting to the ED with an uncomplicated 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 effects*[7].

Topical Anesthetics (for Intact Skin)[5]

Drug	Application	Caution
Emla (lidocaine + prilocaine)	60+ min prior with occlusion	-Vasoconstriction -Rare risk of methemoglobinemia
Lidocaine cream	60+ min prior with occlusion	-Vasoconstriction (venous access?)

Maxilene (Liposomal Lidocaine)	30+ min prior	-Minimally vasoactive

Topical analgesics may also be considered for chronic pain[8].

General Non-Pharmacological Suggestions (as age appropriate)[5,8]

- 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[15]
- Consider psychology/psychiatry consult if necessary
- Physical comfort strategies (e.g. kangaroo care, comfort positioning)
- Distraction (e.g. books, bubbles, TV, breathing, breastfeeding, music, virtual reality, conversation)
- Hot/cold compresses (not for neonates)
- Warm blanket
- Massage
- Activity out of bed
- Elevation
- Splinting, bandaging, dressing
- Injury site pressure

Oral Analgesic Therapies and Dosing[5]

Drug	Dosing	Max Daily Dose
Acetaminophen[#]	10-15 mg/kg/dose every 4-6 hours	75 mg/kg/day Newborn (4-40 wks.): 60 mg/kg/day
Ibuprofen[#]	5-10 mg/kg/dose every 6-8 hours	40 mg/kg/day
Naproxen	2.5-5 mg/kg BID	20 mg/kg/day
Antidepressants (e.g. TCAs), anticonvulsants (e.g. gabapentin)		

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

Alternating between acetaminophen and an 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). Post-operative pain should be dosed as scheduled ("around the clock") and pre-ambulation or pre-procedure (excluding vaccination) analgesics are usually dosed PRN[8]. 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[8].

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 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[2]. 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[6]. 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 pain[12].

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,

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Excellent Resources:

- *Solutions for Kids in Pain (SKIP): https://www.kidsinpain.ca/*
- *Commitment to Comfort: https://www.commitmenttocomfort.com/*

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