



Tools for the Pharmacist Regarding Exempted Codeine Products

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1. Preamble

Canada is currently the world's third largest opioid consumer per capita (including opioids used for acute and palliative pain).¹

Concerns in pain management include delayed and/or under-treatment resulting in increased suffering which may progress to more severe/ refractory chronic pain.² Overt treatment may result in increased adverse effects and hyperalgesia.² A lack of diligence in prescribing safeguards increases the risk of drug misuse, abuse and diversion increasing patient and societal risks.²

Regarding Exempted Codeine Products (ECPs), the onus is on the pharmacist to ensure the product is being used for a recognized medical or dental purpose and on the patient to disclose their last use.³

2. Sales Restrictions of Exempted Codeine Products

Section 7 and 8 of Part J of the Regulatory Bylaws of the Saskatchewan College of Pharmacy Professionals:

Prohibited Drugs

7 No licensed member shall sell a prohibited drug, nor permit or allow the storage of a prohibited drug in a pharmacy under his management. A prohibited drug includes:

- (a) all Exempted Codeine Products offered for retail sale in a solid dosage form including tablets, capsules, gel caps, and other similar dosage forms in a package size exceeding fifty (50) units, and in liquid preparations exceeding package sizes of one hundred (100) ml.

Exempted Codeine Products are defined in section 36 of The Narcotic Control Regulations, (Canada) as those products containing codeine which the public may purchase without a prescription. Such products contain not more than 8 mg or its equivalent of codeine phosphate per solid dosage unit, or not more than 20 mg or its equivalent of codeine phosphate per 30 ml in a liquid preparation. In addition, such products must contain two or three additional medicinal ingredients other than a narcotic in therapeutic proportions. The outer package must also bear the full list of all the active ingredients along with a cautionary notification that the product contains codeine, and should not be administered to children except on the advice of a physician or dentist.

Exempted Codeine Products

8 When a person wishes to purchase an Exempted Codeine Product, only a licensed pharmacist, or pharmacist intern under the immediate supervision of a licensed pharmacist, may sell the Exempted Codeine Products. The licensed pharmacist, licensed pharmacy technician, or intern must document the sale on the patient profile. Except for quantities stated otherwise and pursuant to that authorized by a prescription, the licensed pharmacist, or pharmacist intern under the immediate supervision of a licensed pharmacist, may sell only one (1) consumer package of the Exempted Codeine Product per occasion.

3. Evidence for use of Exempted Codeine Products

Codeine is a weak opioid analgesic used in the relief of mild to moderate pain which is not relieved by non-opiate analgesics.^{4,5} There is insufficient evidence to conclude that any one weak opioid is more efficacious for mild to moderate pain or is associated with fewer adverse events than other weak opioids.⁶ Studies indicate that NSAIDs are equally as effective as acetaminophen/codeine for treatment of acute pain and may be associated with fewer side effects.²

Codeine can also be used, alone or in combination with other antitussives or expectorants, in the symptomatic relief of nonproductive cough.⁵ Codeine and dextromethorphan (DM) have a comparable efficacy in reducing cough frequency.⁴ DM is more effective than codeine in reducing cough intensity. DM produces fewer CNS and GI side effects.⁴

Dosing of antitussives: codeine 10-20mg q4-6h (Max: 120mg/24hr).

4. Analgesics

Table 1: Dosing of ECP Analgesics

| Analgesic | Dose |
|----------------------|------------------------|
| Codeine* | 15-60mg/dose q4-hr |
| Acetaminophen | 500-1000mg/dose q4-6hr |
| ASA | 325-650 mg q4-6hr |

*For relief of mild to moderate pain in adults, the usual dosage of codeine is 30mg every four hours as necessary.⁵

Codeine is converted to morphine via CYP2D6; inter-individual variability can result in differences in the amount of pain relief individuals achieve. Slow metabolizers are unable to convert enough codeine to morphine for analgesic response. Ultra-fast metabolizers have increased risk of opioid toxicity as more codeine is converted to morphine.

Analgesic Ladder¹

Used for both acute and chronic pain

Figure 1: Analgesic Ladder

| | | |
|--|--|---|
| | | Step 3: Severe pain |
| | | Strong opioids + Non-opioids + Adjuvant analgesics |
| Step 1: Mild to moderate pain | Weak opioids + Non-opioid + Adjuvant analgesics | |
| Non-opioids + Adjuvant analgesics | | |

Non-opioid: acetaminophen, ASA, NSAID; Weak opioid: codeine, tramadol, buprenorphine patch, oxycodone- combination; Strong opioid: morphine, oxycodone, hydromorphone, fentanyl, methadone**

**Not for opioid-naïve and generally not used for treatment of acute pain*

5. Rational for the use of Combination Analgesics

Codeine alone is a weak analgesic with very limited effectiveness.⁷ Combining analgesics with different mechanisms or sites of action can allow for reduced doses of competent drugs, reducing overall adverse effects with comparable analgesia.⁵ The combination of two analgesic drugs has the potential to overcome tolerability, efficacy and time-to-onset limitations of the individual drugs and, in certain cases, work synergistically to increase their analgesic effect.⁵

Table 2: Mechanism of Action of ECP Components

| | |
|----------------------|---|
| Codeine | Binds to opiate receptors in the CNS causing inhibition of ascending pain pathways, altering the perception of and response to pain; cough suppression by direct central action in the medulla. |
| Acetaminophen | Not fully understood; inhibits the synthesis of prostaglandins in the CNS and peripherally block pain impulse generation |
| ASA | Irreversibly inhibits COX-1 and 2 resulting in decreased formation of PG precursors |
| Caffeine | CNS stimulant; increases the level of analgesia provided by each agent |

When opiate analgesics are administered in fixed combination with non-opiate analgesics, the opiate dosage may be limited by the non-opiate component .⁵ Care should be taken to ensure that therapy is not duplicated with other OTC preparations and that dosage of the non-opiate drug does not exceed maximum recommended dosages.⁵

6. Codeine Use in Special Populations

Breast Feeding: associated with fatal opioid toxicity in neonate in rapid metabolizers resulting in accumulation of morphine in breast milk.¹

Children: One-third of children cannot metabolize codeine making it ineffective and increasing the risk of side effects.⁹

Elderly: Evidence for effectiveness is lacking and adverse effects, especially constipation are common.⁶

7. Overuse Dangers

Table 3: Adverse Effects

| Ingredient (10) | Daily | Concerns |
|------------------------|--------------|---|
| Codeine* | 360mg | CNS depression, hypotension, respiratory depression |
| Acetaminophen | 4000mg | Acute overdose: hepatotoxicity Chronic daily dosing: liver damage |
| ASA | 4000mg | Upper gastrointestinal events |
| Caffeine | 10-20g | Tremor, restlessness, nervousness, anxiety, insomnia |

* Codeine can be habit forming and can cause serious side effects such as slow heart rate, weak pulse, confusion, hallucinations, seizures and problems with urination. Less severe side effects include dizziness, nausea, vomiting, stomach pain, constipation, sweating and mild rash.

8. Medication Overuse Headache

Acute headache medications may worsen a pre-existing headache disorder when taken too frequently (use of combination analgesics, or opioid-containing medication on 10 days a month or more.¹¹ Patients with a history of migraine appear especially vulnerable to the development of medication overuse headache.¹¹ Differential diagnosis is necessary between medication overuse headache and chronic daily headache (>15 days per month).¹¹

9. Alternative Choices for Common Conditions Treated with Exempted Codeine Products

a) Headaches and Migraines

Table 4: Treatment Options for use in Migraine and Headaches¹²

| Condition | Differential | First line | 2 nd line | 3 rd line | 4 th line |
|------------------------------|--|--|---|--|---|
| Acute Migraine | Headache with two or more of: nausea, light sensitivity, interference with activities | <ul style="list-style-type: none"> ibuprofen 400mg ASA 1000mg naproxen sodium 500-550mg acetaminophen 1000mg | <ul style="list-style-type: none"> triptans antiemetics | triptan plus naproxen sodium 500-550mg | fixed-dose combination analgesics (with codeine if necessary – not recommended for routine use) |
| Tension-Type Headache | Headache w/o nausea and two or more of bilateral headache, non-pulsing pain, mild to moderate pain, not worsened by activity | <ul style="list-style-type: none"> ibuprofen 400mg ASA 1000mg naproxen sodium 500-550mg acetaminophen 1000mg | <p>Adjust lifestyle: reduce caffeine, ensure regular exercise, avoid irregular and/or inadequate sleep or meals, stress management</p> <p>Medication Overuse Headache:</p> <ul style="list-style-type: none"> ergots, triptans, combination analgesic or codeine/other opioid ≥ 10 days a month acetaminophen or NSAIDs ≥ 15 days a month | | |
| Cluster Headache | Uncommon; frequent headaches, severe, <3 hours per attack, unilateral | Refer to ER | <p>Prophylaxis</p> <p>Indicated if headache >3 days/month and acute medications are not effective OR >8 days/month (risk of overuse) OR disability despite acute meds</p> | | |

b) Low Back Pain

Table 5: Treatment Options for Use in Low Back Pain (13):

| | Non-Pharmacotherapy | Acute Low Back Pain | Chronic Low Back Pain |
|----------------------------|--|---|--|
| Differential | Useful in acute, sub-acute, persistent or chronic | Duration: Acute: < 30days; Sub-acute: 30-90 days | Duration: Persistent: 3-6 months; Chronic: >6 months |
| Therapeutic Options | <ul style="list-style-type: none"> Activity as tolerated Physiotherapy Patient education about pain, posture, etc. Heat therapy (acute) <p>*Limited evidence in general: spinal manipulation (most useful for sub-acute), lumbar support, acupuncture, glucosamine, muscle relaxants (effect linked to sedation)</p> | <ul style="list-style-type: none"> acetaminophen 650-1g QID (Max. 4g/day) acetaminophen with codeine 8mg : 2 tabs q4-6h (max 12 tabs per day) acetaminophen with codeine 30 mg: 1-2 tabs q4-6h (max 12 tabs per day) ibuprofen 600-800mg TID naproxen 220-375mg BID opioids if NSAIDs ineffective | <ul style="list-style-type: none"> acetaminophen 650-1g QID (caution with hepatic/renal (MAX: 3200mg/day) long acting opioids in conjunction non-drug therapies tricyclic antidepressants if comorbidities (amitriptyline; other non-TCA antidepressants) <p>Limited Evidence: acetaminophen with codeine, NSAIDs, muscle relaxants</p> |

c) Osteoarthritis

Chronic pain associated with osteoarthritis likely originates from BOTH peripheral and central pain pathways (6).

Table 6: Treatment Options for Use in Osteoarthritis ^{14,15,16}

| Non- Pharmacotherapy | Pharmacological | Important Information |
|---|--|--|
| <ul style="list-style-type: none"> mild-moderate exercise hydrotherapy weight loss if overweight/obese local heat or cold | acetaminophen: IR: 650-1000mg q6-8hr ER: 1300mg q8-12h | DOC if effective |
| | topical NSAIDs | <ul style="list-style-type: none"> topical diclofenac can be equal to oral NSAID for localized arthritis pain capsaicin can help if tolerated topical salicylates do not work for arthritis |
| | NSAIDs: ibuprofen: 400-600mg TID; naproxen: 220mg TID or 375mg BID; celecoxib 200mg daily | <ul style="list-style-type: none"> more effective than acetaminophen for pain but not function consider SE, cost and CIs |
| | glucosamine: 500mg TID (1500mg daily) (most recent studies show limited effect) | <ul style="list-style-type: none"> safe short term; long term safety unknown can take 2 months to see an improvement |
| | intra-articular corticosteroids | Short term benefit in knee |
| | opioids | An option if severe or CI to other medications |
| | duloxetine, TCAs, SNRIs | Inhibit central pain pathways |

DOC: drug of choice; SE: side effects; CIs: contraindications

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