Should codeine and codeine-containing analgesics be removed from the formulary?

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Codeine has been on the market since the 1930's. Codeine has no analgesic properties. Rather, it is a prodrug that is actively metabolized to the opioid morphine by the CYP2D6 (major)/CYP3A4 (minor) enzymes. In August 2012, the FDA issued a warning on the risk of life-threatening adverse events and death when codeine is used to treat post-surgical pain in the pediatric population. Shortly after, the OLOL Children's Hospital P&T approved the removal of codeine and codeine-containing products used for analgesia from the formulary for pediatric patients.

The question posed to the committee is whether this should be removed for adults as well. Here are some reasons to consider removal:

- Approximately 10% of a dose of codeine is actively metabolized to morphine by the CYP2D6 enzyme. Through glucuronidation and CYP3A4 enzyme metabolism, the remaining codeine is metabolized to inactive ingredients.
    - Rapid metabolizers (~2% of the population) quickly convert codeine to morphine, exposing patients to high doses acutely. Poor metabolizers (~10% of the population) do not convert codeine to morphine at a sufficient rate and leave patients with inadequate pain control.
    - When codeine is administered with CYP2D6 inhibitors (e.g. amiodarone, fluoxetine, duloxetine, paroxetine, diphenhydramine, quinidine, and propafenone), the product is slowly converted to morphine and poor pain control is expected.
    - When a CYP3A4 inhibitor (e.g. amiodarone, HIV protease inhibitors, cyclosporine, ketoconazole) is given with codeine, more of the codeine will be diverted for metabolism by the CYP2D6 route and converted to morphine.
- Codeine has not been studied in many large randomized controlled trials.
    - Few head-to-head comparisons of alternatives exist for this drug. In an adult cosmetic surgery population and in two pediatric populations of patients with limb injuries, acetaminophen with codeine was no better than ibuprofen and was associated with more adverse events.
- Codeine has lower affinity for μ-receptors than morphine and reduced effectiveness. Analgesia may be mediated through morphine but codeine receptor occupancy contributes to adverse effects. There is little evidence for the broad belief that codeine causes less adverse effects, such as sedation and respiratory depression, compared with other opioids.

	Codeine Equivalency	
Hydrocodone 5 mg	36 mg	Mild
Hydrocodone 7.5 mg	54 mg	Moderate
Hydrocodone 10 mg	72 mg	Severe

- Other agents are indicated for mild to moderate pain (e.g. acetaminophen, ibuprofen, tramadol)

    - Note: tramadol is also metabolized by the CYP2D6 enzyme and must be metabolized to be activate.
- Approximately 10% of codeine is excreted unchanged in the urine. This puts patients with moderate to severe renal impairment at risk for accumulation of the codeine and it's morphine metabolite.

If removal is supported, the following are additional considerations:

- Review order sets/powerplans. Remove codeine and codeine/acetaminophen analgesic products
    - No change to cough and migraine preparations
- Gain approval for order set/powerplan substitution with alternative analgesics (Note: There is only one order set that we are aware of that contains Tylenol with Codeine on it and based on the parameters, it is used in anyone over 80 years old or patients that cannot tolerate Lortab for any level of pain.)
    - Mild pain: acetaminophen or ibuprofen or 5mg hydrocodone/acetaminophen (Norco)
    - Moderate pain: 7.5mg hydrocodone/acetaminophen (Norco)

References:

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