

Tramadol and Codeine Use In Pediatrics: A Review of Recent FDA Safety Alerts.

Megan Herink, Pharm.D, Drug Use Research and Management, Oregon State University College of Pharmacy

FDA Safety Update

The Food and Drug Administration (FDA) announced in April 2017 that children younger than 12 years should not take tramadol or codeine due to the risk of respiratory depression and death.¹ This announcement expands on FDA labeling updates from 2013 that codeine use is contraindicated in children younger than 18 to treat pain after tonsillectomy or adenoidectomy² and drug safety communications in 2015 warning about the risk of respiratory depression in some children who are rapid metabolizers of codeine or tramadol due to the cytochrome P450 2D6 (CYP2D6) variant.³ A warning was also added to tramadol and codeine drug labeling to recommend against their use in adolescents age 12 to 18 who are obese or who have conditions such as obstructive sleep apnea or severe lung disease which could increase the risk for respiratory suppression with codeine or tramadol (Table 1).¹ Furthermore, the FDA recommends restriction of these drugs for children older than 12 years of age and strengthened its labeling recommendation that breastfeeding mothers not take either drug because breastfed children could also experience potentially fatal respiratory depression. This review will evaluate the evidence behind the recent FDA safety alerts and discuss the place in therapy of these opioids in children.

Table1: Summary of Recent FDA Label Changes for Codeine and Tramadol¹

Contraindications:

- Codeine and tramadol should not be used to treat pain in children younger than 12 years
- Codeine and tramadol should not be used to treat pain after tonsillectomy or adenoidectomy in children younger than 18 years

Warnings

- Avoid use in adolescents between 12 to 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of breathing problems
- Breastfeeding is not recommend when taking codeine or tramadol due to the risks of serious adverse reactions in breastfed infants

Tramadol

Tramadol is an opioid medication that is pharmacologically similar to other opioids but has a lower affinity for μ -opioid receptors and also acts as a weak inhibitor of the neuronal reuptake of norepinephrine and serotonin.⁴ It has been suggested that tramadol has a lower potential of abuse and dependence due to its relatively low affinity for μ -opioid receptor. The affinity for the μ -opioid receptor is 4000-fold less than that of morphine; however, tramadol has still been shown to cause significant withdrawal syndrome which can include both opioid and serotonin-norepinephrine reuptake inhibitor (SNRI) - associated withdrawal symptoms.⁵ Tramadol is a prodrug metabolized via CYP2D6 to O-desmethyltramadol, which has a 200-fold greater affinity for the μ -opioid receptor compared to the parent drug.⁶ Therefore, poor metabolizers often fail to have successful analgesia in response to tramadol and ultra-rapid metabolizers are at a higher risk for side effects due to higher concentrations (Table 2).⁶

Table 2: CYP2D6 Polymorphisms⁶

Phenotype	Prevalence	Clinical Effect
Poor Metabolizer	5-10%	Insufficient Pain Relief
Intermediate Metabolizer	2-11%	Expected analgesia
Extensive Metabolizer	77-92%	Expected analgesia
Ultra-rapid metabolizer	1-2%	Potential for toxicities

In 2014, the U.S. Drug Enforcement Agency (DEA) scheduled tramadol as a Schedule IV substance.⁷ The DEA reviewed available data and concluded that tramadol produces similar pharmacological effects as other opioids, including analgesia and respiratory depression. Since tramadol also inhibits reuptake of serotonin and norepinephrine, additional safety concerns include the risk of serotonin syndrome and an increased risk of seizures.^{5,8} However, the most common adverse reactions with tramadol include nausea, dizziness, and vomiting.

Although tramadol is not approved by the FDA for use in children under 18 years of age, it is commonly used off-label because it is assumed to be safer and less potent than other opioids.⁹ In 2014, nearly 167,000 children in the U.S. received a prescription for a tramadol-containing product from outpatient retail pharmacies.¹ However, there is a lack of evidence for efficacy and safety in this population. A Cochrane systematic review evaluated the effectiveness and side effect profile of tramadol for postoperative pain relief in children and adolescents undergoing surgical procedures.¹⁰ Evidence from 5 trials found that the need for rescue analgesia in the postoperative care unit was reduced in children receiving tramadol compared to placebo (RR 0.40; 95% CI 0.20 to 0.78).¹⁰ However, overall strength of the evidence was low or very low due to small sample sizes, methodological problems, and an inability to perform an accurate risk-benefit analysis since adverse events were poorly reported.¹⁰

Tramadol FDA Warning:

The FDA reviewed data from January 1969 to March 2016 which identified 9 cases worldwide of respiratory depression in children younger than 18 years of age, including 3 deaths.¹ With the exception of a 15-year-old treated for multiple days with tramadol, respiratory depression occurred within the first 24 hours of drug administration.

The 3 fatalities occurred in children younger than 6 years of age. Elevated serum tramadol concentrations were noted in all 3 cases. The indications for tramadol in these 3 children were to treat pain after tonsillectomy, pain after clubfoot surgery, and to manage fever.

In one fatal case where the CYP2D6 genotype was identified, a 5-year-old child was prescribed a single tramadol dose in the evening post-tonsillectomy. A urine sample showed increased metabolite concentrations. Genotyping of CYP2D6 was conducted, and 3 functional alleles were found that were consistent with ultra-rapid metabolism.¹

One non-fatal case involved a 6-year-old who was prescribed tramadol for neuropathy of the hands and feet. After the third dose, the patient experienced respiratory depression and was unresponsive. The patient fully recovered after receiving two doses of naloxone.

Four other non-fatal cases reported in teenagers using tramadol for musculoskeletal pain or sciatica described unresponsiveness or somnolence after one or a few doses of tramadol; all required medical intervention.

A review of the available medical literature for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active metabolite are present in breast milk and caution is advised in breastfeeding mothers.

Codeine

Codeine is another opioid analgesic often combined with acetaminophen for moderate pain relief in adults. Its analgesic effect comes from the demethylation of codeine into morphine. It offers unpredictable analgesia and requires conversion to morphine by CYP2D6. Like tramadol, its conversion is subject to wide genetic variation leading to either poor pain control in slow metabolizers or high risk of overdose in ultra-rapid metabolizers. Codeine is also used to manage cough and is typically combined with promethazine or other cold medications found in over-the-counter products. Codeine depresses the cough reflex by direct effect on the cough center in the medulla. However, there are no well-controlled scientific studies in children, and therefore, the evidence to support efficacy in reducing cough is limited. In 2014, 1.9 million pediatric patients received a prescription for a codeine product from U.S. outpatient retail pharmacies.¹ Of the total pediatric patients, nearly 1.4 million patients received codeine-containing analgesic products, and 483,000 patients received codeine-containing cough-and-cold products.¹ Interestingly, prescriptions for codeine-containing products only slightly decreased in frequency between 2001 and 2010, despite convincing studies documenting their lack of benefit and serious adverse effects.³

Codeine FDA Warning:

The FDA reviewed adverse event reports submitted to the FDA from January 1969 to May 2015 and identified 64 cases of serious breathing problems and 24 deaths with codeine or codeine-containing medicines in children younger than 18 years of age. Fifty of these cases were in children under the age of 12 years. Respiratory depression occurred after a median of 5 doses in these cases (range of one to 18).¹

The most commonly reported products used in reported cases of breathing problems were acetaminophen with codeine used for pain and promethazine with codeine used for cough and cold. Of the 24 deaths, the majority (21) occurred in children under 12 who received codeine for pain post tonsillectomy or adenoidectomy, other post-operative pain, general pain, sore or strep throat pain and cough and cold.¹ There were also numerous cases of excess sleepiness and serious breathing problems in breastfed infants from women taking codeine, including one death. The first case report of a death in a nursing infant from codeine was published in 2006.¹¹

Only 10 cases included information regarding CYP2D6 genotype. However, 7 of the 10 identified cases were ultra-rapid metabolizers, of whom 5 died. The other 3 identified patients were considered extensive metabolizers, which including one death. There were limited data to evaluate an association between codeine or morphine blood levels and respiratory depression. Only 15 of the 64 cases reported drug levels, but 13 were above the therapeutic range.

Summary

Codeine and tramadol are problematic since they are metabolized by the CYP2D6 hepatic enzymes. The prevalence of the ultra-rapid CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not currently available for other ethnic groups.¹

Although the strongest risk of respiratory depression and death are in the ultra-rapid metabolizers of CYP2D6, routine genotyping prior to therapy is not recommended at this time. According to the FDA, this is for several reasons. First, extensive metabolizers may convert codeine to morphine at levels similar to ultra-rapid metabolizers. Also, the positive predictive value of the test is likely low, and the number needed to screen to prevent one event is very high. Lastly, genotyping is difficult to implement routinely.

All tramadol and single-ingredient codeine products are only FDA-approved for use in adults. These therapies should be avoided in children, particularly

those under 12 years of age and adolescents less than 18 years with risk factors for respiratory depression, obesity, obstructive sleep apnea or severe lung disease.

There are several alternative analgesics, including non-opioids that are not affected by CYP2D6 metabolism. Tramadol, codeine, and to a lesser extent hydrocodone and oxycodone all require CYP2D6 for metabolism and could accumulate in ultrarapid metabolizers. Any opioid should be used cautiously in pediatric patients with obstructive sleep apnea. If an opioid is needed, the lowest effective weight-based dose should be used for acute pain on an as-needed basis. Acetaminophen or ibuprofen should be recommended for mild or moderate pain.

For the treatment of cough, patients should be educated that cough is usually self-limiting in children, related to an underlying infection and does not require treatment is important. Additional treatment options include fluids, humidity, and honey for children one year or older. All cough and cold medicines should be avoided in children < 6 years of age since the risk of side effects outweighs benefit.

Peer Reviewed By: Peer Reviewed By: Bill Origer, MD, Faculty, Samaritan Family Medicine Residency and Andrew Gbler, Pharm D, OSU College of Pharmacy Drug Use Research and Management

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