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An update on the safety of prescribing opioids in pediatrics

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Abstract

Introduction: The opioid abuse epidemic and its toll on the adolescent population has heightened awareness for safer opioid prescribing practices in pediatric pain management. Opioids remain the mainstay of therapy for severe pain, although there is an emphasis on multimodal therapy.

Areas covered: In this update, the authors present information on parenteral/oral opioids commonly used in pediatrics. Recommendations for opioid use in special circumstances including neonates and developmental pharmacokinetic concerns are discussed. Due to noticeable interindividual variability, pharmacogenomics may be important for tailoring pain regimens. In particular, the role of CYP2D6 phenotypes on opioid selection/dosing and clinical implications are discussed. A summary of adverse effects and opioid safety data, and the role of regulations, risk assessment, CDC guidelines, follow up and monitoring for compliance in opioid prescribing, are detailed.

Expert opinion: “One size does not fit all” describes the need for public policies focused on pediatric pain and opioid use, as children are not “little adults”. Clinical trials to evaluate pharmacokinetic-pharmacodynamics of opioids are currently lacking. Development of novel biased opioid agonists, clinical integration of genetics in informed decision making, and emphasis on top-down approaches to pain management will be key to decrease opioid reliance.

Keywords

opioid; pediatric; dosing; guidelines; pain management; prescribing

1. Introduction: pediatric pain and current trends in opioid use

Pediatric pain is a significant problem. Studies estimate that 5–38% of youth suffer from chronic pain, with associated annual healthcare costs of \$19.5 billion in the United States (US).[*1] Of about 6 million surgeries that are conducted in children every year in the US,

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Declaration of interest

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[2] in addition to experiencing acute postoperative pain, about 14.5–38% of the children develop chronic post-surgical pain, which has been defined as pain that develops or increases in intensity after a surgical procedure, and lasts for at least 3–6 months after surgery, after exclusion of other causes.[3, 4, 5] Poorly controlled pain in children is a significant problem as 73% of children and adolescents with chronic pain continue to have chronic pain and disability as adults.[6] The approach to pediatric pain management has greatly improved with the implementation of specialized pain programs across the country that focus on both inpatient and outpatient management of acute and chronic pain. There is an emphasis on multimodal analgesia and psychosocial modulation of pain behaviors in both acute and chronic pain settings. However, for the past two decades, hospitals and physicians have been under the pressure of credentialing organization to address and treat pain aggressively. Aggressive, and at times misleading, marketing of pharmaceutical companies contributed to more liberal opioid prescription practices, especially in the field of chronic pain medicine, despite experts pointing out lack of evidence of long term efficacy of opioids in non-acute, non-cancer pain. [7]

From 1994 to 2007, pediatric opioid prescription rates doubled in the US. Cross sectional data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey between 2005–2007 were compared to 1994 data on prescribing controlled medications (opioids, sedatives and stimulants) to adolescents 15 – 19 old and young adults 20–29 years of age. In 1994, controlled medications were prescribed at 2.3 million visits by adolescents and 7.9 million by young adults. In 2007, controlled medications were prescribed at 5.7 million visits by adolescents and 18.6 million visits by young adults. For young adults, the trend for opioids was modest before 2001 and increased considerably after 2001.[**8] An encouraging sign is that between 2010 and 2015, the amount of opioids prescribed in the US has decreased from 782 to 640 morphine equivalents (MME) per capita. This decrease has been attributed to better awareness amongst patients and physicians and publication of national guidelines. However, it is still three times more than in 1999 and four times more compared to European average. [9, 10, 11, 12] This is especially concerning as use of prescribed opioids in high school is independently associated with future opioid misuse among patients with little drug experience.[13] In 2016, 3.6 percent of adolescents aged 12 to 17 reported misusing opioids over the past year, with a twice as high incidence among older adolescents and young adults aged 18 to 25.[14] The dangers of opioid misuse are tied with opioid over prescribing. Opioid prescribing quadrupled between 1999 and 2010 and the rate of opioid overdose deaths rose in parallel with this trend. [15] In 2015, 63.1% of 54,202 death related to drug overdose was related to opioids; 15,000 of these death were related to prescription opioids. [16] [17, 18]

As in adults, opioid misuse has been decreasing through 2017; however, the rate of overdose deaths remains high. In 2015, 4,235 youth aged 15 to 24 died from a drug-related overdose; over half of these were attributable to opioids.[19] Moreover, for every young adult overdose death, there are 119 emergency room visits and 22 treatment admissions.[20] Recent surge in opioid abuse and misuse has prompted recommendations for opioid prescribing from the President's Commission on Combating Drug Addiction and the Opioid Crisis. However, despite the prevalence and relevance to the current opioid epidemic, pediatric pain is often absent from policy and funding initiatives.

2. Pediatric opioid dosing and patient controlled analgesia

Opioids are currently prescribed for acute, subacute, and cancer pain in the pediatric population. The analgesic effect of opioids is primarily due to binding to mu opioid receptors, but some medications also exert their effects through binding of kappa and delta receptors. They are classified into 3 main categories: pure agonists, partial agonists or mixed agonists-antagonists.

2.1. In the acute in-hospital setting, for example postoperative pain and acute on chronic pain conditions (for example, sickle cell crisis pain), options for opioid delivery include as needed interval dosing, fixed or scheduled interval dosing via oral/parenteral routes, and intravenous patient controlled analgesia. Oral route of administration of opioids is preferable for acute pain management but there can be a delay in onset of drug action, decreased drug bioavailability and gastrointestinal effects that may prevent absorption. While there has been an increase in regional and neuraxial analgesia in the pediatric population, PCA (patient controlled analgesia) remains a common method of providing pain control in an inpatient setting in children. Morphine (20 mcg/kg PCA bolus), hydromorphone (4 mcg/kg boluses) and fentanyl (0.25 mcg/kg PCA bolus) are commonly used with or without bolus infusions. Effective analgesia requires a steady state concentration with minimal side effects. The PCA is controlled by the patient if of appropriate age to understand the use of the button (approximately 6 years old and developmentally normal). If the patient is younger than 6 years of age or developmentally delayed, a nurse controlled analgesia (NCA) or caregiver controlled analgesia (CCA) is recommended. Proxy controlled analgesia has been found to provide effective pain relief in children less than 6 years of age, although 1.7% incidence of significant apnea/desaturation reinforces the need for adequate patient monitoring.[21] Alternatives to opioid PCA is an agonist-antagonist opioid PCA, such as butorphanol, in PCA for patients who are sensitive to opioid-induced respiratory depression. Butorphanol is administered in doses of 5mcg/kg bolus and 0–3mcg/kg continuous infusions. Yildiz et al reported that by decreasing the bolus dose by 50% and using a basal infusion, the total opioid consumption was actually lower compared with bolus dosing alone, with no statistical differences in pain, sedation, and nausea scores between the 2 regimens.[22] However, monitoring for potential overdosage remains necessary.[23] These monitors include modified Ramsay or other validated sedation scales, frequent physical assessment, continuous pulse oximetry, respiratory rate and end-tidal carbon dioxide monitoring (capnography), and protocols for early interventions (eg, stopping continuous infusions, lowering opioid doses).

In chronic pain and out-of-hospital settings, opioids are often avoided as they have limited utility in the long term care of these patients due to their side effects, tolerance, and in many cases inability to treat functional or neuropathic pain. In this patient population a functional, multidisciplinary approach to pain management in addition to introducing medications that target neuropathic pain and visceral hyperalgesia are warranted. Some terms and practices relevant to opioid prescribing are described below:

2.2. Opioid rotation:

Extended use of one opioid results in low efficacy for the medication. In these cases, switching to another opioid in an equianalgesic dose may be considered. Table 1 depicts pediatric dosing guidelines for opioids. Opioid rotation is a strategy also used when there is need for a different potency, a lowered opioid dose, use of a smaller quantity, decreased intolerable side effects, allow for use of a different formulation (for example, subcutaneous instead of intravenous), or because of practical considerations such as cost. Due to incomplete opioid cross tolerance, the dose of the new opioid should be decreased by approximately 25–50% to minimize adverse effects and then the dose may be titrated to adequate pain control or supplemented with breakthrough medication doses for rescue analgesia. If the starting opioid has been escalated recently after a prolonged period of stability then a dose closer to the previous stable level may be a more appropriate place to start.[24, 25] In our clinical experience, many appropriate candidates for opioid rotation have chronic use of opioids, and while there are tables to calculate opioid analgesic equivalency these tables are often based on opioid-naïve patients and reflect variable patient populations.

2.3. Opioid equivalent dosing:

Morphine milligram equivalent (MME) is a value assigned to opioids to represent their relative potencies.[26] It is determined by using an equivalency factor to calculate a dose of morphine that is equivalent to the ordered opioid. Some recommendations are to limit new opioid users to <50 MME/day. [26] Morphine equivalent dosing (MED) determines a patient's cumulative intake of any drugs in the opioid class over 24 hours in an effort to help reduce to likelihood of overdose. Tracking daily MED totals can help to: minimize the potential for prescription drug abuse/misuse, reduce the number of unintentional overdose deaths associated with pain medications.

The Centers for Disease Control and Prevention (CDC) has provided updated guidelines pertaining to chronic pain therapy, although they are specifically targeted at patients 18 years and older,[27] and marks an area of significant concern in the pediatric world.[28]. Key goals identified include: defining the effectiveness of opiates, assessing their harm, determining dosage strategies, and minimizing risk. To achieve these goals, they emphasize use of opioid alternative therapies whenever possible, and use of opioids only if benefits outweigh the risks. Meaningful benefit is defined as 30% improvement to pain and function. Providers should limit doses to 50MME or less per day and avoid coadministration of benzodiazepines due to the additive depressant risks. Immediate release medications are preferred over extended release formulations. Ongoing opioid therapy should be closely tracked with urine drug screens and surveillance of state prescription drug monitoring services. Any patient with an opioid use disorder or illegal drug use should be managed with appropriate evidence-based treatment regimens.

To ensure appropriate access to pain management while also addressing the opioid public health crisis, legal restrictions on opioid prescribing were developed. According to the National Conference of State Legislatures (NCSL), as of October 2018, at least 33 states have enacted legislation related to opioid prescription limits. The days of initial opioid

prescription provided ranges from 3–14 days across states, with some states also putting a cap on the maximum morphine milligram equivalents (MME) per day (ranges from 30–100 MME/day).^[**29] Different states also list exclusions to MME cap based on conditions like chronic Pain, cancer, palliative care, hospice care, provider judgment, substance abuse disorder on methadone maintenance therapy, etc.

3. Opioid safety and side-effects in pediatrics

When used appropriately and prescribed by physicians familiar with opioid pharmacology, opioids have been shown to be highly effective and safe for the treatment of many types of pain. Prescribers need to be aware of several side effects related to opioid use that may affect the patient's quality of life. The sensitivity to these effects can vary depending on patient's genetic composition, age, comorbidities, and concomitant medications taken. Overall, the most common adverse effects of opioids include constipation (50% to 65% of patients), nausea (25% to 50% of patients), sedation (20% to 60% of patients), pruritus (2% to 100% of patients, depending upon the route of administration).^[30], as well as myoclonus, and fatigue.

Drug overdose related deaths are mainly due to opioid induced respiratory depression which is the most serious adverse effect of opioids. Opioids act on the respiratory centers of the brainstem, decreasing respiratory drive. Risk factors include increased opioid dose, concomitant pulmonary compromise (eg restrictive and obstructive lung disease), co-administration of other central nervous system depressants (eg sedatives/hypnotics, alcohol), obesity and extremes of age.^[26] In children, respiratory depression has been noted in in-patient postoperative care settings and risk factors identified for naloxone triggering events (including prematurity and developmental delay).^[31, 32] Continuous pulse oximetry and end-tidal capnography has been recommended to closely monitor for respiratory depression especially in high-risk patients. If clinically significant respiratory depression occurs, respiratory support should be provided in addition to administration an opioid antagonist, naloxone. Naloxone can be administered in incremental doses of 1–2mcg/kg. The dosage for total reversal in children five years of age and younger is 0.1 mg/kg, to be repeated every two to three minutes as needed; the dosage for children over five years of age is 2 mg, to be repeated every two to three minutes as needed. Use of pain protocols and standardized order sets in electronic medical record could limit operator error with regards to dosing and improved safety has been demonstrated when PCAs in addition to pain order sets are managed by a dedicated pain service.^[24] In addition, genetic risk factors for opioid induced respiratory depression have been identified which are detailed in the section on opioid pharmacogenomics.

Constipation is another common side effect of both weak- and strong-opioid use.^[33] Opioids bind on the receptors in the central nervous system and enteric plexus within the gastrointestinal smooth muscles and cause decrease in gastrointestinal peristalsis. Patients should be encouraged to increase fluid intake, fiber ingestion, and ambulation and prophylactic bowel regimen should be initiated for all patients on opioids. In addition, three peripherally acting μ -opioid receptor antagonists (alvimopan, methylnaltrexone, and naloxegol) which target the μ -opioid receptor without reversing analgesia are US Food and

Drug Administration approved. A literature review of the efficacy of these drugs in treating opioid-induced constipation or postoperative ileus found that they may be effective but low quality of evidence prevented definitive conclusions.[34]

The emetogenic side effect of opioids is due to three mechanisms: stimulation of central chemoreceptors in medulla, enhanced vestibular sensitivity and delayed gastric emptying. [35] The treatment for nausea and vomiting involves symptomatic management. The first line of treatment are serotonin receptor antagonists such as ondansetron. Other treatment options include anticholinergics (scopolamine, meclizine), dopamine receptor antagonists (metoclopramide, prochlorperazine) and atypical antipsychotics (olanzapine). Pruritus is believed to be mediated through the central mu-opioid receptors, central stimulation of receptors or histamine release or cholestasis induced by opioids. This can result in significant discomfort and dissatisfaction. Management includes use of opioid agonists-antagonists like nalbuphine which has been recommended as first-line treatment choice[36], low dose naloxone (0.25–1.65 mcg/kg/hr) or naltrexone infusions, antihistamines, serotonin receptor antagonists, propofol and dopamine D2 receptor antagonists.[37].

Chronic opioid use has also been linked to tolerance to opioid effects, hyperalgesia, physical dependence, immunosuppression, and hypogonadism. Opioid tolerance is defined as the need to increase the dose to maintain the equipotent analgesic effects.[38] This, however can exacerbate the occurrence of the side effects. Opioid tolerance occurs earlier in younger age groups, develops during critical illness after prolonged infusions of short-acting opioids.[39] The challenge of balancing adequate analgesia and risk of side effects in prescribing opioids is a major concern. Strategies such as slow titration of dose, use of non-opioid adjuvant analgesics, symptom management of the side effect, opioid rotation, and/or changing in route of administration can help. [40] Adjuvants (such as acetaminophen, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants and antispasmodics), may effectively decrease the dose of opioid required for effective analgesia and minimize opioid related side effects. Importantly, differential tolerance to opioid effects with higher tolerance developing for opioid analgesia compared to respiratory depression is a major concern when opioids are administered to chronic opioid users for acute pain conditions as this increases their risk for serious side effects (due to increased need for opioid doses for analgesia).[41] It is important to use alternative analgesia for opioid-tolerant patients to minimize need for opioids.

4. Opioid dosing in special situations

In certain pediatric disease states where drug absorption, distribution, metabolism, and elimination are altered, pharmacokinetic and pharmacodynamics properties necessitate opioid dosing changes to avoid adverse effects.

4.1 Neonates:

Opioid pharmacokinetics are affected in neonates due to low plasma protein concentrations and a higher body water composition which affects drug distribution, immature metabolic processes and low hepatic enzyme activity, affecting clearance resulting in a prolonged half-life, compounded by reduced renal excretion due to immature glomerular filtration, tubular secretion, and reabsorption.[42] However, limited data are available on the

pharmacodynamic behavior of drugs in the pediatric population although immature blood brain barrier might result in increased sensitivity to opioids. Use of mechanism based pharmacokinetic-pharmacodynamic models to characterize opioid exposure-response relationships using patient-specific predictors of inter-individual variability (age, sex, organ maturity etc.) may be important for clinical translation and efficacy.[43] Based on population pharmacokinetic model in newborns, including preterms, infants and children under the age of 3 years, a loading dose in $\mu\text{g}/\text{kg}$ and a maintenance dose expressed in $\mu\text{g}/\text{kg}^{1.5}/\text{h}$, resulted in a 50 % dose reduction in maintenance doses in neonates <10 days compared with traditional dosing.[44]

In relation to the opioid crisis there has been a five-fold increase in the incidence of babies born with Neonatal Abstinence Syndrome (NAS) between 2000 and 2009.[45] Between 2000 and 2009, the incidence of NAS among newborns increased from 1.20 (95%CI,1.04–1.37) to 3.39 (95%CI,3.12–3.67) per 1000 hospital births per year (P for trend <.001). Antepartum maternal opiate use also increased from 1.19 (5%CI,1.01–1.35) to 5.63 (95%CI,4.40–6.71) per 1000 hospital births per year (P for trend<.001). [45] NAS is defined as a postnatal opioid withdrawal period in neonates born to mothers who used opioids during pregnancy. Symptoms typically present within 2–7 days of birth and are dependent on multiple factors, including type of opioid used and most recent use by the mother. Symptoms range from small tremor and irritability to GI issues such as vomiting and diarrhea to fevers and seizures. There are grading scales available such as the Finnegan NAS score that utilizes a numbering system to guide diagnosis and treatment.[46] Newborns with NAS stay in the hospital for an average of 16.9 days (compared to 2.1 days for other newborns), adding cost to the hospitals of an estimated \$1.5 billion annually. [45, 47]. In terms of treatment, conservative therapy (low stimulus environment, swaddling and holding, and non-nutritive sucking) is successful in 30–40% of cases but should symptoms persist, an opioid, typically morphine or methadone, should be initiated at a weight based dose of 0.05mg/kg q3hr with escalation of dose by 0.02mg/kg if scores are above threshold (>8 in the Finnegan scoring system). Maintenance at the stabilization dose should persist for 48 hours prior to initiating the wean. Opiates are then weaned in a stepwise fashion, typically 10% decrease daily until they are no longer needed. Patients should be monitored for 48 hours in the hospital off opioids prior to their discharge .[48]

4.2. Liver failure-

Children with liver cirrhosis develop gastropathy which results in delayed gastric emptying and delayed gastric absorption.[49] Patients with ascites and edema have an increase in volume of distribution of the drug. It is therefore prudent to start with lower initial doses of hydrophilic opioids (ex. morphine, oxycodone and hydromorphone) and slowly titrate to effect.[50] Changes such as hypoalbuminemia, impaired hepatic extraction, impaired biliary excretion, impaired renal excretion (such as in hepatorenal syndrome) and decreased CYP enzyme activity, all result to an increase in serum drug concentration.[51] Thus, dose adjustments are needed to avoid drug accumulation and its complications. Morphine, oxycodone, tramadol and hydromorphone should be used at reduced doses and prolonged intervals of administration. Fentanyl appears to be safe in patients with modest hepatic dysfunction. Meperidine is not recommended since the toxic metabolite normeperidine may

accumulate especially for patients with renal insufficiency. Table 1 is a summary of the recommendations for opioids in patients with hepatic impairment.

4.3 Renal impairment-

Infants have reduced renal function compared to older children and young adults. Great caution should be exercised when prescribing opioids in infants and patients with chronic kidney disease (CKD). Increased risk of adverse effects occurs due to accumulation of toxic or active metabolites, altered drug distribution, decreased drug binding, increased sensitivity to central nervous system side effects, and increased permeability of the blood brain barrier. The use of hydromorphone, oxycodone, hydrocodone, methadone and fentanyl appear safe but renal dose adjustment maybe necessary. Methadone and its metabolites do not accumulate significantly in patients with renal insufficiency.[52] Although fentanyl is a potent synthetic opioid and follows the same pattern of drug elimination as other opioids, its metabolites are inactive and non-toxic.[45] Morphine, meperidine, tramadol and codeine are not recommended due to accumulation of their toxic metabolites in renal failure.[52, 53] Table 1 summarizes the recommendations of opioid use for CKD patients.

4.4 Obesity, obstructive sleep apnea (OSA) and difficult airway-

The prevalence of OSA in children is 1–4%; [54] with a higher prevalence in severe obesity. [55] In severe OSA, there is an up-regulation of μ -opioid receptors due to recurrent hypoxemia.[56] Thus, administration of opioids and concomitant sedatives increases the risk for respiratory depression, increased pharyngeal collapse, and exacerbation of obstructive symptoms in these situations. Dosing considerations for opioids in obese children requires consideration of opioid pharmacokinetics and dosing weights. Lean body weight (LBW) is the most appropriate dosing scale to use especially that their cardiac output is significantly correlated to LBW. Multimodal analgesia with non-opioid analgesics and regional techniques are preferred to reduce the opioid use in these patients.[57] “PK mass”, which is correlated to lean body mass, has also been proposed as a scalar for dosing patients spanning weights of 40–210 kg, as it correlated linearly with fentanyl doses needed to maintain analgesia.[58] It is especially prudent to cautiously titrate opioids in these patients. Similarly, special precautions are also given to patients with known difficult airway or at risk of upper airway obstruction (e.g facial and neck edema). Opioids and other sedating medications should be cautiously given due to risk apnea and desaturation. Vigilant monitoring is critical. A multimodal approach to pain control is preferred to decrease opioid use. Whenever possible, local infiltration and peripheral nerve blocks be considered in these patients.

4.5 Opioids for fetal surgery:

Contrary to prior belief, nociception begins in the early stages of fetal development. Due to advances in fetal surgery in addition to the timing of these surgeries in the 2nd and 3rd trimester, pain control for the fetus is justified. Fetal stress in response to painful stimuli has been shown by an increase in cortisol, noradrenaline, and beta-endorphin in fetuses of 20–34 weeks gestation (3). Our practice is to administer fentanyl to the fetus alongwith atropine and muscle relaxant either intramuscularly or intravenously when the fetus is delivered on uteroplacental perfusion during ex-utero intrapartum procedures.

5. Opioid individualization and pharmacogenomics

Choosing a particular opioid is based on pharmacokinetic factors such as route of administration, duration of action, metabolism, and side effect profile. Once administered, opioids are redistributed to skeletal muscle, CNS, kidneys, lungs and primarily undergo hepatic metabolism and to a lesser extent renal metabolism. Pharmacokinetics of all opioids can differ within a patient (intraindividual variability) and between patients (interindividual variability), and this variability is often due to both environmental and genetic factors (4). Medication regimens should be patient-specific, patient-centered and individualized based on clinical findings. Routine clinical practice follows the trial and error strategy of prescribing the minimum quantity of opioids anticipated to be necessary for the expected severity and duration of pain (for opioid naïve patients). There is a growing base of knowledge regarding opioid pharmacogenomics and the effects of genetic variants on opioid analgesia and side effects, which makes it imperative for clinicians to be aware of them. Twin studies have demonstrated the heritability for opioid effects[*59, 60]. Pharmacogenomic effects occurs due to altered metabolism, altered receptor mechanics and/or transport of opioids in the liver or the blood brain barrier. Table 2 provides an overview of the different genes implicated in the pharmacokinetics of opioids. We will focus our discussion here on salient genes influencing pharmacokinetics (*CYP2D6*) and pharmacodynamics (opioid receptor *OPRM1*).

5.1 CYP2D6:

This gene belongs to the cytochrome P450 super family and more than 100 variants have been described. (<http://www.cypalleles.ki.se/cyp2d6.htm>) [61]. While *CYP2D6*1* is the wild-type allele; variants affect activity of the gene (Table 3) [61, 62, 63]. An activity score is assigned to each allele in the diplotype (0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The predicted metabolizer phenotype is defined by the sum of the two scores:

- Poor Metabolizer (PM) has an activity score of 0
- Intermediate Metabolizer (IM) has an activity score of 0.5
- Extensive Metabolizer (EM) (normal) has an activity score of 1 to 2
- Ultrarapid Metabolizer (UM) has an activity score greater than 2

5.1.1 Codeine: The role of *CYP2D6* phenotypes came into prominence after deaths/near deaths reported with “standard” doses from oral codeine in UM of *CYP2D6* [64, 65].

Codeine is a prodrug and is converted to dangerously higher concentrations of morphine in UM. Fatality was reported in an infant who was breastfed by his UM mother who was taking codeine[66], in a healthy 2-year old boy given codeine two days after adenotonsillectomy [64] and several post-surgical children especially in the presence of sleep apnea/obesity, who were prescribed codeine. [67, 68, 69]. Fifty year review of adverse events in children who had codeine-containing products showed 64 cases of severe respiratory depression and 24 deaths mostly in children younger than 12 years of age[70]. This has led to clinical practice guidelines and regulations regarding use of codeine by the World Health Organization

(March 2011)[71], US Food and Drug Administration (FDA) (August 2012)[72], European Medicines Agency (EMA)[73] and Health Canada (June 2013)[74] and the UK Medicines and Healthcare Products Regulatory Agency (July 2013 updated in April 2015)[75]. Restrictions were placed on use of codeine in children under the age of 12 years, after adeno-tonsillectomy procedures.[76] In 2013, the joint FDA advisory committee recommended amendment of the codeine label to include a “black box warning” contraindicating codeine treatment of pain and cough in all children <18 years of age and to remove codeine from the Over-the-Counter monograph.[77] The 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP2D6* genotype and codeine therapy [78] suggest using alternative analgesics to codeine in patients who are *CYP2D6* poor for better efficacy and UM for safety reasons.[**79] Clinical consequences and recommendations for codeine dosing provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) are summarized in Table 3. Although most fatal cases were reported in young children with sleep-disordered breathing, after tonsillectomy procedures, codeine may not be safe in other pediatric populations also. Pediatric codeine use has declined very slightly from 1.08 to 1.03 million children prescribed codeine from 1996 to 2013.[80] With pediatric obesity on the rise and the likelihood of undiagnosed sleep disorders, alternative opioids should be considered with an emphasis on non-opioid for postoperative analgesia must be carefully considered. Future education of health care providers and parents about safe use of opioids, improved policies and further research is necessary to improve safety of pediatric postoperative analgesia.[81]

5.1.2 Tramadol: Similar caution has been issued for tramadol, a weak opioid agonist that is metabolized minimally through *CYP2D6*-mediated oxidation to O-desmethyiltramadol, with 200-fold greater affinity for μ -opioid receptors than the parent drug[82] after a recent report of tramadol induced respiratory depression in a child who was a *CYP2D6* UM [83].

5.1.3. Oxycodone: In addition, oxycodone, a commonly used opioid also undergoes O-demethylation by *CYP2D6* (10%) to oxymorphone and noroxymorphone, [84] which are 14 and 10-times more potent than the parent compound [85]. The data on the effects of *CYP2D6* on oxycodone are however inconclusive.

5.1.4. Hydrocodone: Hydrocodone is 12 times more potent at the opioid receptor than codeine[85] and is metabolized by *CYP2D6* and *CYP3A4*, into an active metabolite hydromorphone, and norhydrocodone, respectively. *CYP2D6* UM may thus have up to an eightfold greater plasma concentration of hydromorphone, whereas PM receive minimal analgesia [86]. In response to occurrence of >400 cases of adverse events associated with its use between 1969 and 2005, the US FDA has banned the sale of more than 200 hydrocodone products, as it a common component of antitussive medications [87].

5.2. Mu opioid receptor *OPRM1*

is a G protein-coupled receptor widely distributed in the periaqueductal gray area, substantia gelatinosa area in dorsal horn of spinal cord, in the olfactory bulb, cerebral cortex and the amygdala. The most extensively studied variant is the A118G SNP on exon 1 [88]. which

causes substitution of an adenine (A) with a guanine (G) at base 118, leading to amino acid exchange at position 40 from asparagine to aspartic acid (N40D). The loss of a N-glycosylation site in the extracellular region of the receptor[89] is accompanied by reduced opioid receptor binding potential[90, 91, 92, 93] In accordance, several studies in adults and children have shown that opioid requirements (morphine, M6G, fentanyl and alfentanil) were greater and the adverse effects such as nausea/respiratory depression less in postoperative patients and volunteers with the GG/AG genotypes compared with those with the AA genotypes at the A118G SNP[94, 95, 96, 97, 98, 99, 100, 101, 102]

5.3. Genetic risk for addiction:

In addition, the risk of addiction from opioids is about 40–60%.[103] *5-hydroxytryptamine (serotonin) 2A receptor gene (HTR2A)* genotypes at SNPs rs6313 and rs6311, variants of the glutamate receptor, *N-methyl D-aspartate 2A (GRIN2A)* gene that encodes the 2A subunit of the N-methyl D-aspartate (NMDA) receptor, *Dopamine D1 receptor (DRD1)* and the OPRM1 A118G have been shown to be associated with alcohol dependence,[104] heroin addiction,[105] and opioid dependence respectively.[106, 107, 108]

Although clinical translation of opioid pharmacogenomic findings are not yet routine, precision medicine based on pharmacogenetically informed prescribing is becoming more feasible as genotyping costs decline. Recent studies have evaluated genetic test informed clinical decision making for outcome improvements. A prospective study in non-cancer pain patients genotyped for pain perception-related catechol-O-methyltransferase haplotypes showed that physicians adjusted treatment plans for 40% of patients. When medication changes were made based on genetic testing results, 72% of patients showed improvement in clinical status.[109] While ethical implications and cost-effectiveness is debated and considered limiting steps to clinical implementation, genetic precision in prescribing opioids could streamline the costs associated with pain polypharmacy, as has been shown in other areas.[110, 111]. Similar trials are underway in adults with chronic pain. The Precision Medicine Guided Treatment for Cancer Pain is a pragmatic clinical trial that seeks to determine the utility of *CYP2D6* genotype-guided opioid prescribing in patients with cancer. [112] In children, implementation of pharmacogenetics-based codeine prescribing that accounts for *CYP2D6* metabolizer status for pain management in sickle cell disease showed safety and efficacy.[113]

6. Prescribing opioid practices and regulations

Pendulum has swung from under to over prescribing of opioids over the past decades, leading up to opioid crisis we are facing nowadays, claiming thousands of lives every year. Pediatric and adolescent patients have not been immune to this problem. Consequences such as increased rate of newborns with neonatal abstinence syndrome (NAS), increase in unintentional exposure, unintentional overdose, recreational use, morbidity and mortality, and rate of ED visits have been reported.[45] Between 1994 and 2007, adolescent (15–19 year old) and young adult (20–29 year old) opioid prescribing doubled, while these age groups were also most likely to abuse prescription drugs. [**8] It is important to understand the source of prescription opioid abuse to be able to prevent it. Adolescents gain access to

opioid through prescription or diversion. Among youth aged 12 to 17, 3% reported past-month nonmedical use of prescription medications; 50% of high school students reported using an illicit drug by graduation; 19% of illicit drug users started by misusing prescription opioids. [114] 63.2% of adolescents used opioids from other sources than own prescription (purchased on internet, from family, friend, or purchased from drug dealer). [115] Hence, it is of paramount importance to restrict the availability of opioids for misuse, while gingerly balancing the need to treat pain.

6.1. Restricting indications for opioids:

Restricting indications of opioids to severe pain situations can guide effective opioid prescribing. Such situations include acute postsurgical pain of 5–7 day duration; acute traumatic injury, persistent postoperative pain, epidermolysis bullosa, cerebral palsy, sickle cell disease. In 2007, a controlled medication was prescribed in 5.7 million adolescent primary care visits (15–19 year old) and 18.6 million young adult office visits (20–29 year old) versus 2.3 and 7.8 million in 1994 respectively. Between 2005–2007, 9.6% prescriptions were for non-injury and 14.5% for injury related visits in adolescent patients. The main indication was musculoskeletal and back pain (19%), followed by injury (12%). Controlled medication was prescribed in 1 out of 9 visits in adolescents. Although increase in opioid prescriptions does not necessarily mean increase in misuse, over the years there has been a trend in increase in controlled substance misuse by adolescents. Physicians must use judgment and caution when prescribing opioids and determining length of treatment and quantity of opioids. [**8] (expert opinion)

6.2 Regulations

In 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) implemented new pain management standards for inpatient and outpatient medical care (Phillips DM, JCAHO pain management standards are unveiled). Pain scores became a key performance indicator and hospital-wide initiatives brought pain management to the forefront of medical care. With an emphasis on appropriate pain management and frequent documentation of pain scores in all age ranges, increased opioid availability along with the potential for adverse effects, toxicity, and abuse became a concern. In January 2018, JCAHO published revised set of pain management recommendations with emphasis on implementing non pharmacologic means to alleviate pain. [116]

6.3 Risk assessment –

Several tools have been used and some validated to assess risk for opioid misuse and abuse – e.g. RAFFT, DAST-A (Drug Abuse Screening Test – Adolescents), POSIT, CRAFFT. [117, 118] [119] This is an important step as it determines level of monitoring. High risk patients can be prescribed opioids, but must be monitored closer than low risk patients. For example, they receive only weekly supplies of medications, they are drug screened every visit, they can be called in randomly for pill count in between the visits. The tools vary from provider to self-administered, detailed to brief. CRAFFT has been validated for adolescents and opioids, other tools are not validated or not for opioids specifically (alcohol). [120, 121] In our practice, we use Opioid Risk Tool (ORT) which is a tool designed to screen and predict substance related aberrant behavior and has been validated in adult patients (Figure 1). We

chose it for our practice as it is brief, self-administered and easy to interpret. We utilize it for triaging purposes to determine the need for close monitoring. [122] The best practice is to choose one tool and apply it consistently to all patients; regular medical record audits would assure prescriber's compliance that at the end benefit patient care and increase safety.

6.4 Informed consent:

In our practice, patients are prompt to sign informed consent when prescribed opioids on an outpatient basis. The consent serves as an instrument to educate patients and parents about the risks and benefits of opioid use, including misuse, abuse and addiction. The interactions with other prescription and over-the-counter medications is discussed, with emphasis on sedative side effects. Certain states (e.g. Ohio) require every patient to sign it before initiation of opioid therapy. [123]

6.5 Opioid agreement –

serves as a tool explaining rules of engagement if more than a 5–7 days prescription is required. It has been a standard tool for us to use, a routine part of the packet for safe opioid prescribing practices. It is also required by our state regulations. It identifies the medical office responsible for prescribing opioids. If patient presents frequently to various emergency rooms or different medical offices to renew prescriptions, it may be a sign of “doctor shopping” and opioid misuse. The rules need to be set for lost or stolen prescription which raise red flags and concerns for misuse. In our practice, we do not replace lost or stolen prescriptions, we do not provide early refills. Patients are instructed to either visit Emergency department for signs of withdrawal, or are prescribed clonidine to mitigate those. Patients are encouraged to designate one pharmacy for all their prescription needs. Patients also agree with monitoring for compliance (see below). Ideally, patients are seen monthly, however, some of our pediatric patients come from distance and monthly visits are not feasible. In our state we are permitted to prescribe up to 3 months of opioids. Our internal practice has been 1 month and then patient needs to be seen. Although there are no guidelines whether and how often the opioid agreement and Informed consent should be renewed, it is a good practice to do it yearly. Renewal presents a good opportunity to educate the patients about the risks and benefit of opioids and to offer options for non-opioid, non-pharmacologic analgesia.

6.6 Storage and disposal –

Having safe place for medications where traffic of strangers or access to young children is limited or eliminated is critical. For moderate and high risk patients, parents will dispense and have control over the opioids. Lock box, private space for medication storage are appropriate for high/moderate risk patients. If the medication is discontinued or opioid changed, the leftover medications must be dispensed according to state law. Certain pharmacies have collection boxes where medications can be dispensed safely.

7. Follow up and monitoring of compliance of opioid use

Opioid related events in pediatric pain medicine can be linked to parental or patient factors. Parents in charge of opioid administration to children present additional challenge for

providers in situations where diversion by parent is suspected, but cannot be directly addressed due to privacy rules restrictions. Series of tools need to be implemented in clinical practice to safely manage pediatric patients who are prescribed opioids and are part of broader initiative in Risk Elimination and Mitigation Strategies.

7.1 Follow up –

schedule is determined by risk assessment, state regulations and individual practice. For low risk patients, follow ups are scheduled on a monthly basis, but can be extended up to 3 months in certain states. In our practice, patients are seen monthly if they are within 1 ½ hour of medical center and every 2 months beyond that. Patients are strongly encouraged to engage their local pain physicians or primary care physicians if long term opioids are required, with our availability to consult and collaborate on as needed basis. This is especially true for out of state patients as many pharmacies would not fill out of state prescriptions. For moderate and high risk patients, weekly or biweekly visits are warranted. All patients are required to present their pill bottles for pill counts, even if empty, and not only for opioids, but also adjunct medications.

7.2 Side effects –

are discussed and documented in electronic medical record every visit

7.3 Monitoring of compliance –

is facilitated by two tools – random urine drug screen (UDS) and pharmacy report. UDS monitors presence of prescription and illicit substances in patient's urine. The discrepancies such as missing drug or metabolites (with caveat that it may not reach the triggering threshold for positive if patient took low dose or many hours elapsed since the last dose), presence of different than prescribed drug or metabolite, or presence of illicit substance should trigger conversation with the patient and family. When in doubt or lab error suspected, the test is repeated immediately. If non-compliance is evident, then further plans must involve weaning and referral to addiction specialist. Many times there are other risk behaviors present (losing prescriptions, running out early, many pharmacies used to fill scripts) that support non-compliance finding and warrant opioid wean. In terms of frequency, different states and pharmacy boards differ in their requirements for UDS; common practice is 4 times a year, no more than 3 months apart. The UDS and regular review of pharmacy electronic reports are required by state regulators and enforced by state medical and pharmacy boards (see below). Noncompliance can trigger practice audits by these boards, or even DEA.

7.4. Risk Elimination and Mitigation Strategies (REMS):

Pharmacies are playing an active role in implementation of REMS for opioid prescriptions. They are able to generate reports for each patient including medication, quantity, calculation of morphine equivalent dose and flagging if it exceeds limits for a given state (e.g. 30 mg morphine equivalent/day in Ohio), prescriber, pharmacy filling the prescription, etc. Again, it is one of the tools that can alert provider about doctor shopping, pharmacy shopping or

other issues. The reports can be generated for several states for patients living close to state line, potentially visiting out of state providers.

7.5. Quality improvement –

managing safe opioid prescribing practices can be time consuming and labor intensive. However, it also helps streamline patient care with having standardized processes in place. Any element can be a target for quality improvement project. From implementation of consent or agreement, to monitoring provider's compliance with the process via chart audits, etc.

8. Setting up treatment goals, realistic expectations and exit strategies

Efforts to reduce opioid prescribing through guidelines, prescription drug monitoring programs, and limits on days' supply do not appear to have affected prescribing for adolescents as much as desired.[124] Hence, certain other factors are required on this front. In pain medicine, the ultimate goal of any treatment is improvement in function. Yes, ideally, the pain would go away altogether, but it is not always possible. As a matter of fact, this is more of an exception than the rule, and many times is achieved at the expense of side effects or complications. In acute situation, function translates into getting out of bed, early ambulation, compliance with incentive spirometry, oral intake, etc. In chronic pain, function reflects attending school, participation in extracurricular activities or community events, ability to carry on with age appropriate activities of daily life. This is where education and setting realistic expectations about pain relief and function plays an important role and must take place.[125] Our message is consistent and emphasizes return of function before pain resolution; this is very much true for chronic pain situations, but can be applied in acute situations as well.

Functional disability inventory (FDI) is a validated 15 item, self-administered inventory, measuring effects of pain on daily function. [126] It ranges from mild to severe pain related disability. Pain coping efficacy is another tool to measure patient's ability to effectively cope with pain. In our practice, FDI is administered at every visit – whether it is for acute, persistent postoperative pain or chronic pain - and provides valuable information and trends in patient's ability to function. The treatment is then adjusted accordingly. It is a reliable tool, however, in certain cases can be misleading. Example would be a poorly motivated, sedentary adolescent who – when asked if the pain prevents her/him from running the length of football field – answers 'NO' which would indicate full ability to do so, whereas, in fact, it can mean "Pain doesn't bother me to run the length of the football field, I just don't do it".

Multimodal analgesia along with multidisciplinary care are gold standard for treatment of pain. If in rare circumstances opioids are utilized on long term basis, the goals of the treatment must be established, documented and assessed at every visit (usually monthly), and again, with functional gains being the priority. There must be clear understanding with the family that if the goals are not achieved or there is no change in function, the opioids will be weaned off. Occasionally, what patients and families hear is that no pain medications will be provided. In reality, patient remains in our care and we continue to utilize non-opioid and non-pharmacologic means for analgesia.

9. Conclusion

Opioid prescribing is a complex task that requires dedication of all involved and having good processes in place. In addition to medication management, there is a host of regulations providers are expected to comply with. Although no universal recipe how to manage controlled substances exists, many tools have been developed, validated and successfully implemented in routine practice. With appropriate indications, screening for patients at risk for misuse and abuse, education with informed consent and opioid agreement, regular follow ups, compliance checks and more education, this task can be tackled successfully and seamlessly. Studies looking at efficacy of safe opioid practices are lacking, but much needed. Additionally, controversies exist even to this date whether CDC guidelines and revised JCAHO guidelines will harm certain patient populations. Other ongoing debate has involved implications of medical use of cannabis, where interplay between controlled substances and medical cannabis being unclear. Use of novel PK/PD modeling and quantitative systems pharmacology approaches might allow tailoring opioid dosing to minimum effective doses, to allow true personalization in pediatric opioid dosing. [127]

10. Expert opinion

There are major information gaps in opioid prescribing practices and education in pediatrics. Pediatric clinical trials are needed to inform focused consensus guidelines and policy initiatives geared towards opioid prescribing in children. There is still a scarcity of PK/PD studies on opioid use in pediatrics. Bedside translation of PK-PD assisted real-time technologies and education about allometric dosing approaches instead of routine weight-based approaches to dosing may be more attuned to pharmacokinetic parameters and evidence. Hospitals and clinics would benefit from having task forces to ensure implementation of policies and regulations to maintain compliance among all pediatric providers. While there are state mandates limiting opioid prescriptions and drug monitoring programs, there is a need to control the swing towards minimal prescribing in situations of acute pain, as poor control of pain increases the risk of development of persistent pain conditions and can drive the patient towards seeking illegitimate opioids. With marijuana legislation and possible opioid-cannabinoid interactions as well as increased use of alternative medications like gabapentin for neuropathic pain, it will be important to ensure one addiction is not replaced by another. One path to improved pain medicine practices could involve a combination of behavioral and genetic risk signatures in conjunction with sophisticated decision support algorithms in perioperative and chronic pain treatment settings to prescribe the right opioid, or in some cases, an opioid alternative, in the right dose for each individual patient. Research investment into systems biology and other -omics based technologies in determining opioid effects may be important for development of novel therapeutics. Advanced pharmaceuticals that avoid activation of the beta-arrestin pathways that prevent tolerance to opioid effects may be in early trials but will not be available for wider use for at least 7–9 years. Increased stress on alternative non-opioid management strategies for pain and top-down approaches to effectively manipulate pain related behavioral mechanisms would go a long way to prevent opioid addiction in the future.

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Article Highlights

- Opioid prescribing rates, opioid misuse and mortality from opioid abuse are on the rise in adolescents, which makes careful prescribing of opioids an important responsibility of all health care providers.
- The authors provide information for the safe use of commonly used parenteral and oral opioids in the pediatric population.
- The authors discuss opioid use in special populations, including neonates and other systemic conditions like obesity and renal failure which influences the metabolism and effects of opioids.
- The authors review the importance of pharmacogenomics on opioid selection and dosing, with a special emphasis on CYP2D6 implications for opioid dosing, and warnings against use of codeine in the pediatric population
- The role of regulations, risk assessment, follow up and monitoring for compliance in opioid prescribing has been discussed in detail with an overview of authors' practices as a guideline.

Figure 1.

A flow diagram for guidance of opioid prescribing and compliance monitoring is presented. Besides opioids, the emphasis on alternative pharmacological and non-pharmacological methods which are necessary to consider to decrease opioid reliance are also depicted. ORT: Opioid risk tool. REMS: Risk Elimination and Mitigation Strategies. NSAIDs: Non steroidal anti-inflammatory drugs

Table 1. Opioid potencies, pediatric opioid dosing and dose adjustment recommendations in patients with liver and renal disease.

Opioid	Equianalgesic Dosing (mg)		MME conversion factor	Active metabolites	Pediatric dose		Renal disease implications	Liver disease implications	Other implications
	IV	PO			IV	PO			
Morphine	10	30	1	Morphine-3-glucuronide Morphine-6-glucuronide	0.1mg/kg/dose	0.3mg/kg	Avoid in CKD (CrCl<30ml/min) and dialysis patients	Reduce dose and frequency by 50%	
Fentanyl	0.1-0.2	-	0.13-0.18	Norfentanyl	1-2mcg/kg/dose		No clinically significant accumulation in CKD	None	
Hydromorphone	1.5	7.5	4	Dihydromorphone Norhydromorphone Hydromorphone-3-G	0.015mg/kg/dose	0.03mg/kg/dose (young children) 2-4mg per dose in older children	Dose reduction required	Limited data	
Meperidine	100	300	0.1	Normeperidine	1mg/kg/dose		Contraindicated in CKD and dialysis patients	Avoid use	
Oxycodone	-	20	1.5	Oxymorphone Noroxymorphone		0.1-0.15mg/kg	Dose adjustment recommended	Reduce dose	
Methadone	10	10	3	Methadol Normethadol	0.1mg/kg/dose	0.1mg/kg/dose	Dose adjustment recommended in patients with severe impairment	Dose adjustment recommended in patients with severe impairment	potential to cause a prolonged QT interval
Tramadol	-	120	0.1	O-desmeth tramadol			Max dose 100mg every 12hrs (CKD) and 50mg every 12hrs in dialysis patients	Avoid use	Is also a norepinephrine and serotonin uptake inhibitor – serotonergic syndrome likely if used alongwith SSRI
Tapentadol									

MME, morphine milligram equivalent; CrCl, creatinine clearance; CKD, chronic kidney disease; SSRI: selective serotonin reuptake inhibitor

Table 2: Common relevant liver enzymes, opioid substrates, their inducers and inhibitors, and common polymorphisms with effect on enzyme activity

P450 Enzymes	Selected substrates	Inducers	Inhibitors	Variants	Effect on enzyme activity	Developmental consequences
CYP2B6	Methadone, Meperidine	Carbamazepine (S), phenobarbital, phenytoin, rifampin (S), efavirenz (W)	Clonidogrel (W), ticlopidine (W) Prasugrel (W)	*6(s16G>T, 785A>G) *16*5 (172H-262K-487C)	Decreased	
CYP2D6	Codineine dextronemethorphan Oxycodone Hydrocodone tramadol	None known	Bupropion (S) Fluoxetine (S) Paroxetine (S) Quindine (S) Duloxetine (M) Amitodarone (W) Cimetidine (W) Celecoxib (W) Methadone (W)	*3, *-8, *11,-*16, *19,-*21, *38, *40, *42 (inactive) *1, *2, *35 (functional / wild-type) *9, *10, *17, *29, *36, *41 (decreased activity)	2 Nonfunctional alleles (PM) 1 reduced functional allele or 1 active allele (IM) 1 or 2 functional alleles (EM) Multiple functional alleles (UM) in the absence of inactive or decreased activity alleles	Delayed maturation under 2 years – reaches adult values by 1-2 years – poor metabolizer phenotypes as neonates, compounded by variants
CYP3A4 CYP3A5	Morphine Meperidine Fentanyl Sufentanil Remifentanil Alfentanil methadone	Carbamazepine (S) Efavirenz (M) Nevirapine (M) phenobarbital phenytoin (S) phenobarbital phenytoin (S) pioglitazone rifabutin (W) rifampin (S) St. John's Wort (S) Aprepitant (W) Prednisone (W)	HIV antivirals (S) Ketoconazole (S) Clarithromycin (S) Erythromycin (M) Grapefruit juice (M) Verapamil (M), diltiazem (M) aprepitant (M), Atorvastatin (W), cimetidine (W), Isoniazid (W) Oral contraceptives (W)	CYP3A4*1B CYP3A5*3 CYP3A4*1G	Increased Nonfunctional Decreased	Delayed maturation under 2 years – reaches adult values by 1-2 years
UGT2B7	Morphine	-	-	rs7668258 (211 C/T) rs7439366 (802 T/A)	Lower enzyme activity, but no clinical consequence identified	Deficient in neonates and infants – reaches adult values by 1-2 years
OCT1	Morphine transport into hepatocytes			Arg61Cys (rs12208357), Gly4401Ser (rs34130495), Gly465Arg (rs34059508) and the deletion of Met420 (rs72552763),	morphine clearance in homozygotes of loss-of-function OCT1 variants (OCT1*2,*5/*2,*5) was significantly lower; increased tramadol plasma levels	
ABCC3	Morphine metabolite transport out of hepatocyte			Allele A at rs4148412 and allele G at rs739923	Increased formation clearance of morphine glucuronides and respiratory depression	

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4>; <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>

Strong inhibitor: >5-fold increase, Moderate inhibitor: 2-5 fold increase, Weak inhibitor: <2- fold increase in the AUC of a substrate

Strong Inducers: 80% decrease, Moderate Inducers: 50-80% decrease, Weak Inducers: 20-50% decrease in AUC of a substrate

PM: Poor Metabolizer; IM: Intermediate Metabolizer; EM: Extensive Metabolizer; UM: Ultrarapid Metabolizer.

CYP: Cytochrome P450; UGT: Uridine Glucuronosyl Transferase; OCT: Organic cationic transporter; ABC: ATP Binding Cassette

Table 3.

CYP2D6 polymorphisms, classification of phenotypes based on effect on activity and recommendations for codeine therapy

Likely phenotype. ^a	Activity score	Examples of diplotypes	Implications for codeine metabolism	Recommendations for codeine therapy. ^b	Classification of recommendation for codeine therapy	Considerations for alternative opioids
Ultrarapid metabolizer (~1-2% of patients)	>2.0	*1/*1xN, *1/*2xN	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity. ^{d,e}
Extensive metabolizer (~77-92% of patients)	1.0-2.0. ^c	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Normal morphine formation	Use label recommended age- or weight-specific dosing. [#]	Strong	
Intermediate metabolizer (~2-11% of patients)	0.5. ^c	*4/*10, *5/*41	Reduced morphine formation	Use label recommended age- or weight-specific dosing. [#] If no response, consider alternative analgesics such as morphine or a non-opioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer (~5-10% of patients)	0	*4/*4, *4/*5, *5/*5, *4/*6	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided

^a: Frequency estimates in Caucasians

^b: CPIC Guidelines 2014

^c: some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and define patients with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients (Lotsch 2009 morphine)

[#] Although theoretically extensive and intermediate metabolizers will not develop high morphine concentrations from codeine conversion, since genetic testing is often clinically infeasible, the evidence for risks associated with its use are compelling enough to recommend against use of codeine in routine practice.

<https://www.pharmgkb.org/guideline/PA166104996>

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