TREATMENT OF CHILDREN'S PAIN: ANALGESICS

Pediatric Pain Resource Nurse Curriculum

Ann & Robert H. Lurie Children's Hospital of Chicago

The MAYDAY Fund

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Objectives

- Explain principles for treating children's pain with pharmacologic therapies.
- Describe how developmental differences influence use of nonopioids, opioids, co-analgesics, and adjuvant medications in pediatric pain treatment plans
- Develop pediatric multimodal pain treatment plans that demonstrate knowledge of age-related considerations, mechanism of action, indications, route, contraindications, and adverse effects of pharmacological therapies.

Why Are Children with Pain Not Treated Like Adults?

How are analgesics selected and dosed for children as compared to adults?

Type your answer here.

Principles of Pediatric Pharmacologic Treatment

Develop a pain treatment plan

Cure sometimes, treat often, comfort always.

~Hippocrates

Cause of pain, disease, treatments, and procedures, including surgery, provide guidance for developing pain treatment plans. This may be the only guidance available to manage pain in critically ill, pre-verbal, and nonverbal neonates, infants and children..

In the future, genetics of pain sensitivity and pharmacogenetics may also provide predictive guidance to use when planning individualized pain treatments.

Both now and in the future, self-report of pain, pain location, quality and severity will provide additional guidance to develop individualized treatment plans for patients able to provide self-report.

Treat pain based on cause, type, site, and severity

Develop realistic pain treatment goals. Focus on:

- Pain relief or reduction
- Functional recovery or functional restoration

Pain can not always be completely relieved, but pain can be controlled to optimize function.

Develop an age and developmentally-appropriate multi-modal pain treatment plan

Multimodal analgesia is the use of a variety of analgesics and biobehavioral (nonpharmacologic) techniques. Multimodal analgesia may provide greater pain relief at lower analgesic doses, resulting in fewer adverse analgesic effects than can be achieved with single medication therapy. Use of more than one analgesic or method of relieving pain may also address individual genetic differences in pain sensitivity and drug metabolism.

Key assessments for developing a pain treatment plan

Past/current pain control methods and their effectiveness

Previous experiences with pain management influence views about pain and pain management. Review current treatments for pain with the child and family. Inquire about home remedies, over-the-counter medication use, complementary, and alternative therapies.

Pain Control Method (examples, not an exhaustive list)		
Pharmacologic	Over-the-counter drugs Neuropathic pain medications Opioids	
Physical	Physiotherapy Transcutaneous electrical	Cold/heat nerve stimulation (TENS)
Psychologic	Relaxation Cognitive behavioral therapy	Distraction
Integrative Medicine, Complementary & Alternative therapies	Massage Traditional therapies Chiropractic care	Acupuncture Herbal Yoga

Assess for multiple sites, causes, and types of pain

Obtain a comprehensive medication and pain treatment history

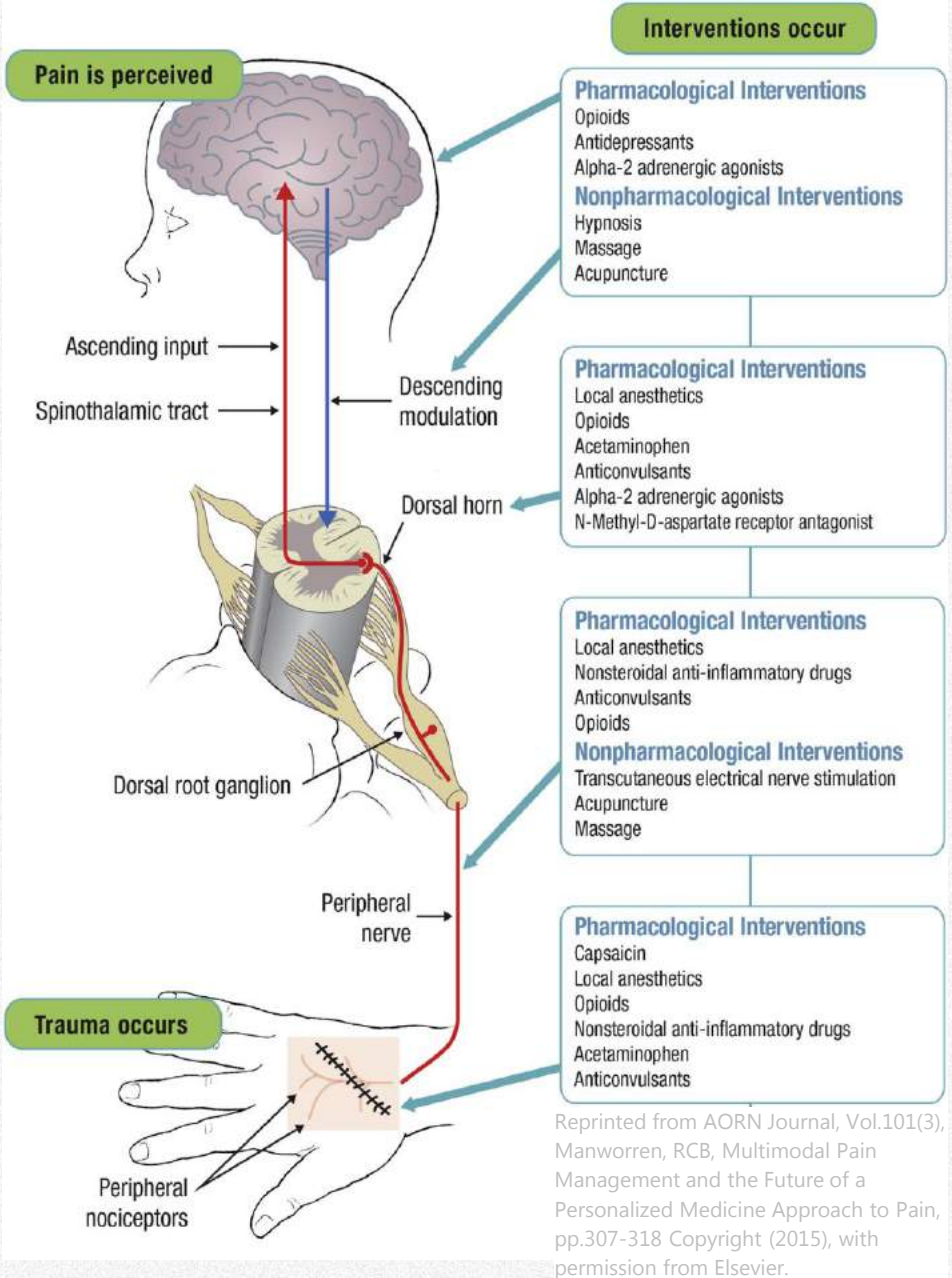
- Medications and treatments tried
- Efficacy and response
- Adverse effects, including allergies
- Concurrent treatment with other medications and potential drug-drug interactions

Identify drug-related fears that may lead to:

- Inadequate or under-treatment of pain
- Poor treatment adherence

Pain treatments and interventions

The effect of pharmacological and biobehavioral pain management interventions along the nociceptive pain pathway is illustrated at the point that each intervention exerts its mechanism of action to relieve pain.



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Develop a pain treatment plan

Pharmacokinetics is what the **body** does to the **drug**.

Pharmacodynamics is what the **drug** does to the **body**.

Pharmacogenetics is the influence of **individual allelic** differences and associated variability in medication responses.

Pharmacogenomics involves the **entire genome** associated variability in medication responses.

Pharmacokinetics involves the movement of the drug into, through, and out of the body:

- Absorption of the drug, including bioavailability
- Distribution throughout the body and tissues
- Metabolism includes the chemical reactions that change drugs into compounds (metabolites) that are easier to eliminate. There are 3 possible outcomes from phase one metabolism:
  1. The drug metabolites are pharmacologically inactive.
  2. One or more of the metabolites are pharmacologically active, but less so than the original drug. (i.e., Morphine)
  3. The original substance (prodrug) is not pharmacologically active, but one of its metabolites is (i.e., Codeine and morphine metabolite)
- Excretion, or removal of the drug from the body

Pharmacokinetics is the relationship between time and the concentration of drug at various sites in the body.

Pharmacokinetics is dependent on patient-related factors and the drug's chemical makeup.

Pharmacodynamics involves the effects of the drug on the body measured by receptor binding and dose-response curves

Pediatric differences

Failure to provide analgesia results in "rewiring" of neural pathways (also known as plasticity) as well as perceived increased pain.

For example, research in newborns not provided analgesia during circumcision demonstrated an exaggerated response to immunizations

Nociceptive pathways are developed by birth (20-24 weeks gestation) but inhibitory mechanisms are not well developed.

- Neonates have a wider receptive area at the dorsal horn and lower excitatory threshold.

Neonates have:

- greater GI surface area to body weight ratio, which results in greater absorption, although gastric emptying is
  - ➢ time delayed for the first 6 months of life
  - ➢ decreased by GERD, prematurity, and high caloric feeds
  - ➢ increased by human milk
- reduced absorption of fat soluble drugs due to reduced bile acids
- increased drug absorption through the skin since absorption is related to skin thickness
- increased blood brain barrier permeability, which may result in greater central nervous system effects from opioids.

Protein binding differences in neonates result in more unbound opioids.

Pediatric differences

Hepatic enzymes and renal clearance are immature in neonates:

- The cytochrome 450 (hepatic) enzymes system reaches adult capabilities by 1 year of age.
- Higher serum levels with slower drug clearance may require lower dosages and longer intervals between doses.
- 3-10 year olds have the greatest metabolism, which then begins to drop off during adolescence.
- Renal clearance is about 50-75% at 6 months of age but is not fully mature until 1 year of age.
- Slower renal clearance means longer duration of action, so intervals between doses should be extended.
- If renal function is poor, medications that are renally eliminated may need to be dose adjusted based on estimated clearance. For example, morphine's metabolites (active and inactive), accumulate in renal impairment, so consider an alternative opioid such as oxycodone which does not have active metabolites that accumulate in renal dysfunction.

Implement pain treatment plan

Give adequate doses

- Pediatric patient doses are based on weight, age, and sometimes body surface area
- Time treatments based on duration of analgesia
- There are many drug dosage recommendations available for pediatric patients, but there are many more drugs that have not been studied in the pediatric population.

Dosing recommendations may be empirical or extrapolated from adult dosing.

Pediatric dosing is not "one-size-fits-all," and may need to be adjusted based on response and adverse effects.

Reassess pain regularly and document assessment

Nurses should administer analgesics at intervals consistent with analgesics' durations of action.

Because of individual variability of responses to drugs, nurses should determine the duration of action of analgesics by evaluating patient response and maintaining vigilance for return of pain.

Evaluate treatment efficacy and document evaluation

- Titration of analgesia and changes to the treatment plan should be based on evaluation of treatment effectiveness and reassessment of pain.
- Taper and discontinue medications that are ineffective or result in intolerable adverse effects that are likely to prevent the achievement of pain treatment plan goals

Pediatric obesity

Obesity is defined as 85th percentile or above for BMI.

One third of children and adolescents are considered obese.

Medications are dosed based on weight in pediatrics, however, dosages calculated by weight may actually exceed recommended adult doses.

- Most adult analgesic doses are based on a weight of 50-60 kg.
- Use adult dose recommendations for pediatric patients who weigh more than 50 kg.

When the child is obese, dose corrections should be considered even if the dose calculated by weight does not exceed adult doses, especially in narrow therapeutic index medications.

Although there are not standards or risk/benefit studies to guide dose adjustment for overweight and obese children, several methods have been suggested:

- *Ideal body weight = 50% BMI for age x height (in meters)* ^{2}
- *Adjusted body weight.* Adjust weight based dose by a specific medication cofactor to account for excess body fat (Ross, et al, 2015).

Obese patients can be at increased risk for respiratory depression when opioids are dosed based on their actual weight.

Implement pain treatment plan: Other pediatric considerations

Since medications are dosed based on weight, a tablet or capsule is not "one size fits all". Always take into consideration the dosage being prescribed as well as whether the patient will take the form (liquid or tablet) of the medication.

Dosage forms available

- Oral suspension, tablet, capsule, orally disintegrating, sublingual. Bitter medications can often be masked with citrus, so mixing in orange juice can help. Chocolate syrup is another agent that can be used to mask taste.
- Topical
- Intravenous,
- Avoid IM. The IM route is painful and dangerous due to erratic absorption and potential for patient injury

Dosing schedule

Consider frequency and challenges to schedule adherence like school, sleep, and timing around meals.

Availability & Affordability

- Some prescription medications and most over-the counter medications are not covered by insurance
- Many oral suspensions are not commercially or readily available and may need to be extemporaneously compounded

Pancreatitis

What is your multimodal pain management plan?

Consider both pharmacologic and nonpharmacological interventions.

Patient: 3 year old female (14kg)

PMH: cerebral palsy, g-tube, NPO, non-verbal, and recently diagnosed with pancreatitis

Pain regimen: morphine IV every 4 hours PRN, acetaminophen IV every 6 hours PRN and is on her last dose of IV ketorolac every 6 hours (total 48 hours of therapy).

Parents report that she is in constant pain (abdominal), not sleeping at night, gagging and is not tolerating feeds prior to being NPO. She is only comfortable in the fetal position or when being held.

rFLACC scores range from 4-8/10

Analgesic Categories

Evaluate pain treatment plan

Medications used in pain treatment plans are often categorized by:

- type of pain being treated, such as neuropathic or chronic
- pain severity, such as mild, moderate, or severe
- as prescription or over-the-counter.

These categories represent old-fashioned pain treatment philosophies that do not provide guidance for developing pain treatment plans.

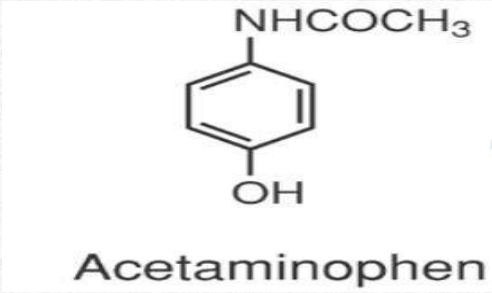
Implement pain treatment plan

The mainstays of analgesia are non-opioids and opioids. However, there are many other medications commonly included in plans to treat pain, associated symptoms and conditions, and analgesic side effects. These medications may or may not have analgesia as a primary treatment indication.

Non-opioids	Opioids	Co-analgesics or Adjuvant Analgesics	Other Adjuvants
• Ceiling of analgesia • Examples: acetaminophen and NSAIDs (nonsteroidal anti-inflammatory drugs)	• Historically considered not to have a ceiling of analgesia • Examples: Morphine is the prototype	• Analgesia may or may not be the primary indication for these drugs • Ceiling of analgesic effect or adjuvant effect • Examples: local anesthetics, antidepressants and anti-seizure drugs	• Used to treat related problems, such as insomnia, depression, and anxiety • Used to treat analgesic adverse effects, like opioid-induced constipation

Non-opioids

Non-opioids: Acetaminophen



Many patients will say

"Acetaminophen doesn't work"

Assess this statement further.

What does "working" mean for the patient?

Acetaminophen is a potent around the clock analgesic .

Patients may not "feel" the effects as they would with an IV opioid.

Does it reduce or relieve their pain?

Acetaminophen has been one of the most commonly used analgesic and antipyretic medications around the world

Indications

- Antipyretic,
- Analgesic
- No anti-inflammatory or antiplatelet activity

Mechanism of action:

- Involves central and peripheral COX enzyme inhibition
- Possibly acts on serotonergic inhibitory descending pathway and endogenous opioid pathway
- Central cannabinoid system antinociception processes

Dosage forms available:

- oral (suspension, chew tab, ODT, tablet)
- rectal
- IV

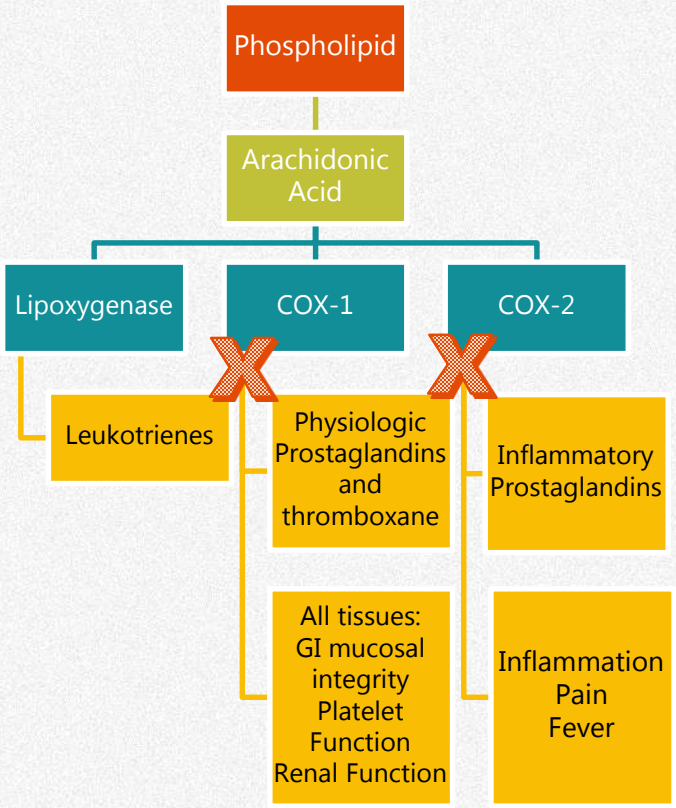
Dose Guidelines

- Well tolerated within therapeutic dosage range
- Metabolized primarily in the liver
- Toxicity when recommended daily limit is exceeded (4g or 75-90mg/kg)

In 2011, the FDA recommended lowering the maximum daily dose from 4 to 3 Grams and required manufacturers to limit the acetaminophen content to 325 mg per dosage unit.

This may result in less than the pediatric therapeutic dose of 10-15mgkg.

Non-opioids: NSAIDs



The diagram is an attempt to simplify the arachidonic acid pathway and explain where NSAIDs work and why they cause adverse effects

Indications

- Antipyretic,
- Analgesic
- Anti-inflammatory

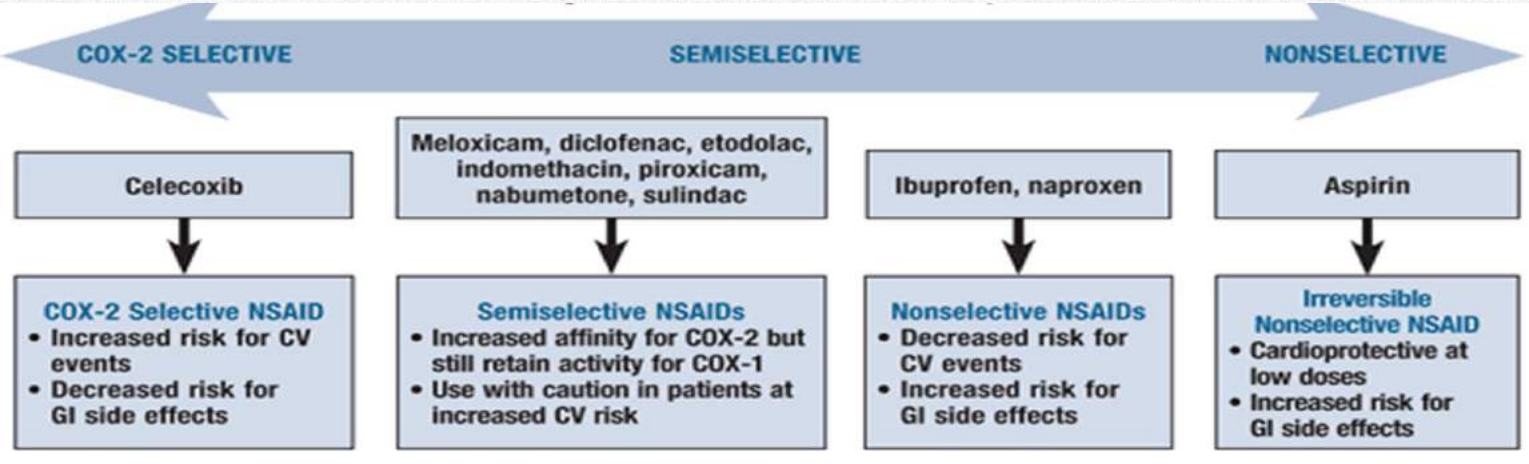
Mechanism of action:

- Reduces activation and sensitization of peripheral pain receptors
- Inhibits cyclooxygenase (COX) enzyme which inhibits the production of prostaglandins and thromboxane which dilate blood vessels to cause inflammation and pain.

The extent of COX enzyme inhibition varies among NSAIDs

- Inhibition of COX increases leukotrienes.
- COX -1 is critical in maintaining the integrity of platelets, normal renal function, and GI mucosa. Associated adverse effects from inhibiting COX-1 (ibuprofen, ketorolac), include GI bleeding, impaired renal function, and platelet inhibition
- It was thought that COX-2 inhibitors could control pain, inflammation, and fever without the adverse effects of nonselective COX inhibitors . However, adverse cardiac effects made COX-2 inhibitors fall out of favor.

Non-opioids: NSAIDs



There is a maximum dose.

The dose, drug interactions, and adverse effects vary for NSAIDs.

When choosing NSAIDS, the primary considerations are adverse effects, convenience, and cost.

Pediatric studies suggest NSAIDs may be more effective than opioids for bone pain (Drendal, et al, 2009).

NSAIDs have different selectivity for the COX enzymes.

- The risk of **GI adverse effects** is increased with concomitant factors such as taking on an empty stomach, underlying GI disease (IBD) or additional medications that can change gut pathology (steroids).
- **Renal toxicity** is most commonly seen in patients with additional risk factors such as underlying renal dysfunction, dehydration, concomitant nephrotoxic medications, hypotension, or hypovolemia. In patients at risk, monitor renal function regularly.

NSAID Contraindications.

NSAIDs should not be used in patients with low platelets (patients receiving chemotherapy) or patients at risk for bleeding.

Animal studies show delayed bone healing associated with NSAID exposure. However, pediatric studies indicate NSAIDs do NOT impair bone healing in children or adolescents. (Sucato, et al., 2008; Vitale, et al., 2003; Kay, 2010; Horn, et al, 2010).

Non-opioids: NSAIDs

Ibuprofen:

- decreased absorption < 2 years,
- use longer frequencies in infants less than 3 months

Ketorolac: metabolism is similar to adults by 1 year of age

Reye's syndrome seems to be triggered by using aspirin to treat a viral illness or infection, such as chickenpox or the flu.

Reye's syndrome is a rare but serious condition with swelling of the liver and brain.

Signs and symptoms of Reye's syndrome, such as confusion, seizures, and loss of consciousness, require emergency treatment.

NSAID	Pediatric Dosing	Interval
Aspirin	*Aspirin is not recommended for pediatric patients due to the risk of Reye's Syndrome.*	
Choline magnesium trisalicylate	10-20 mg/kg oral *Adult max= 3 Gms/day*	8-12 hrs
Ibuprofen	4-10 mg/kg *Adult max =3200mg/day*	6-8 hrs
Naproxen	5-10 mg/kg *Adult max =1250mg/day*	8-12 hrs
Ketoprofen	25-50 mg	6-8 hrs
Indomethacin	0.3-1 mg/kg *Adult max = 200mg/day*	6-8 hrs
Meloxicam	0.125 mg/kg *Adult max = 15mg/day*	24hrs
Ketorolac	0.5 mg/kg IV *Adult max = 30mg/dose*	6 hrs
Diclofenac	1 mg/kg *Adult max = 200mg/day*	8 hrs
Celecoxib	10-25kg: 50mg BID >25kg: 100mg BID *Adult max = 200mg BID*	12-24 hrs

Opioids

Pancreatitis, continued

What pediatric differences need to be taken into account in developing this patient's treatment plan?

Patient: 3 year old female (14kg)

Pain regimen: patient has been on IV hydromorphone for 3-4 weeks. Dosing has escalated during this time period.

- *Total daily dosage of hydromorphone = 3 mg or 3000 mcg per day*
- *POSS = 1*
- *FEN: G-tube feedings are being tolerated*
- *Primary service requested conversion to oral/g-tube medications*

Opioids or Narcotics?

Words are powerful and shape attitudes and behaviors

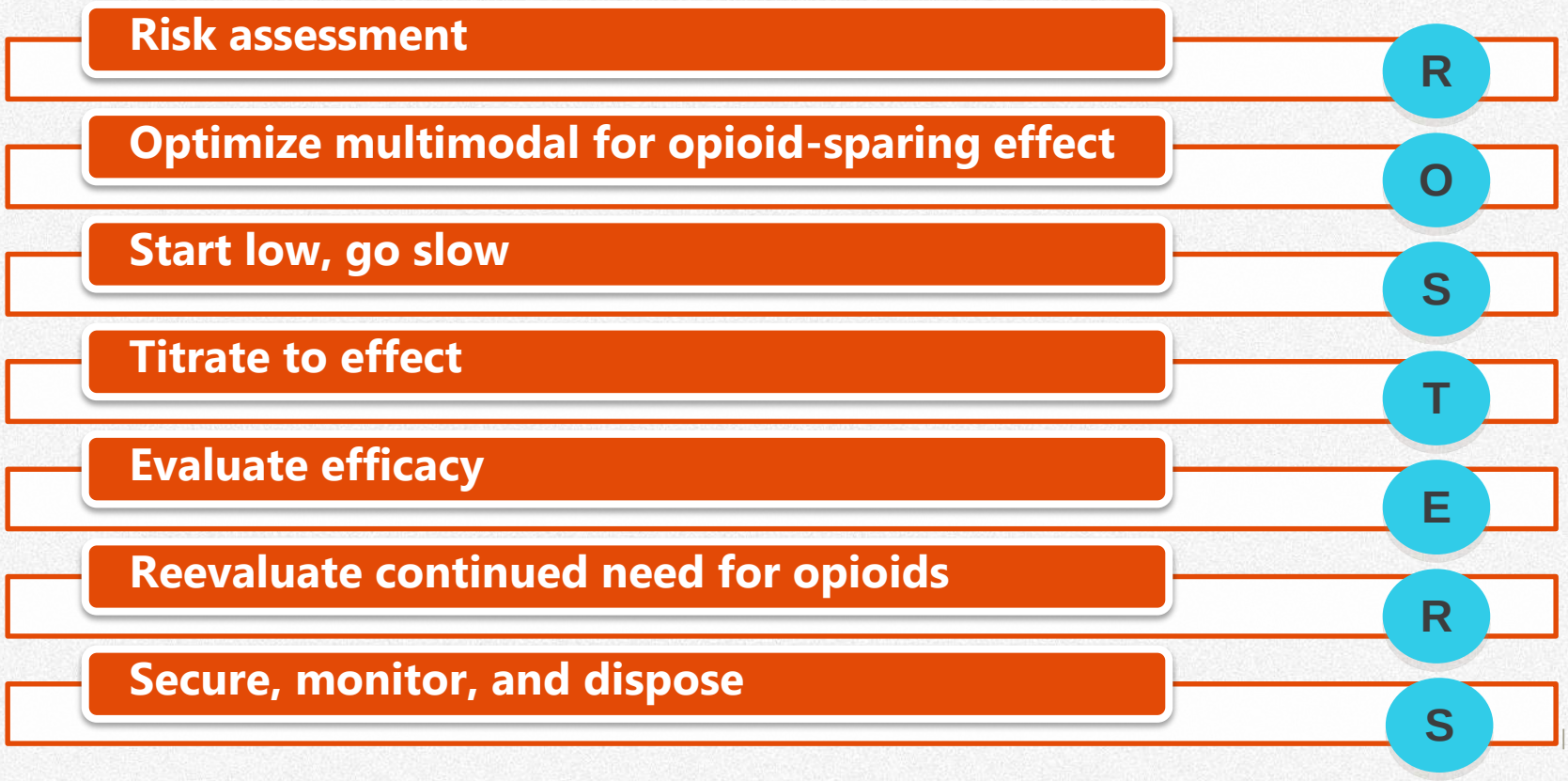
Opioid analgesics have abuse potential and are addictive. The abuse potential of opioids must be discussed with patients and the words used by healthcare professionals can help to distinguish scientific, legal, pain and substance use disorder concerns.

Opiate	Medications derived from the opium poppy, Opiates include morphine and heroin
Opioid	Includes all synthetic, semi-synthetic, and natural compounds that act by binding to the mu, delta, and kappa receptors in the central and peripheral nervous systems
Narcotic	Derived from the Greek word for stupor; but now associated with opioids and used in a legal context to refer to drugs that are abused
Agonist	Binds to a receptor to activate the receptor to produce a biological response
Antagonist	Binds to a receptor to block or dampen agonist-mediated responses

Opioid ROSTERS

When opioid treatment is appropriate

- Optimize multimodal approach.
- Start with the recommended initial dose for size and age and titrate slowly to effect.
- Evaluate efficacy and reevaluate continued need for opioids to treat pain
- Educate patients and families in the risk of unintentional death from opioid misuse and monitor the patient.



Opioid ROSTERS

Risk assessment

- Neonates, obese children, and patients with obstructive sleep apnea are at greatest risk for respiratory depression from opioids.
- Consult an addictionologist to co-treat family of any child who requires treatment with opioids and has a history or family history of substance abuse
- Opioid risk assessment tools are available, but have not been validated for children; and don't actually predict opioid misuse or abuse. They merely identify common characteristics of individuals with opioid use disorder, such as family history of substance abuse and co-existing psychiatric illness.

Optimize multimodal approach for opioid-sparing effect

- Considered local anesthetics and scheduled non-opioids

Start low, go slow

- Treat with the lowest effective opioid dose
- Neonates should start at 25-33% of the recommended pediatric starting opioids dose.

Titrate to effect

Evaluate efficacy

Reevaluate continued need for opioids

Secure, monitor, and dispose

- Advise patients and parents that sharing opioids is dangerous and can lead to unintended death
- Advise parents to secure opioids at all times, monitor their children's use and promptly dispose of opioids that are no longer needed to avoid accidental ingestion or unintentional misuse.

Opioids

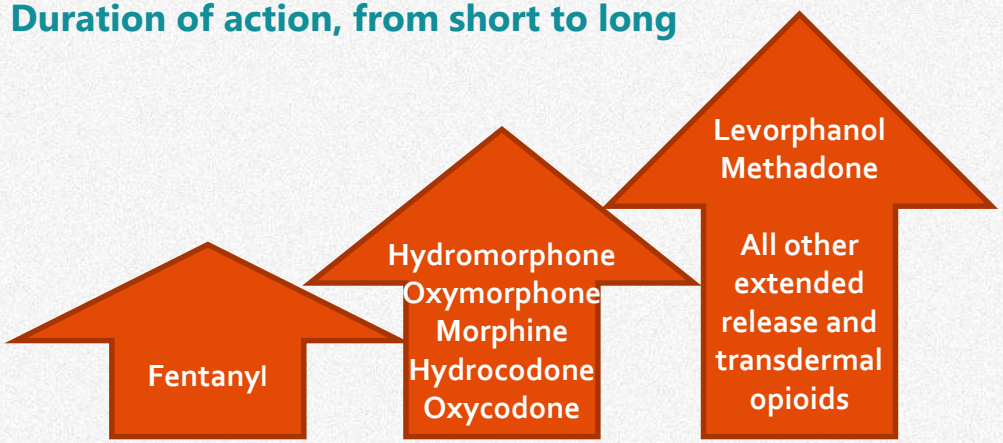
Opioids are indicated for pain and considered a 2nd line interventions on the World Health Organization (WHO) analgesic ladder

Many different opioids exist and are available in a wide variety of dosage forms.

Indications

- Analgesic
- Effective for both nociceptive and neuropathic pain

Duration of action, from short to long



Mechanism of action

- Opioid receptors are distributed throughout the brain, spinal cord, peripheral nervous system, skin, and joints.
- Opioids mimic the actions of endogenous opioid peptides by interacting with opioid receptors designated mu (μ), kappa (κ), and sigma (σ).
- Opioids have multiple sites of action, including: medulla, spinal cord, spinal trigeminal nucleus, and periaquaductal grey (PAG) which is an integration modulation site from peripheral nerves to the central neuraxis.
- In the brain, opioids activate descending pain inhibitors
- Opioids alter limbic system activity to modulate sensory and affective aspects of pain.

Opioids provide pain relief by:

- Decreasing pre-synaptic release of excitatory neurotransmitters
- Decreasing post-synaptic neuronal excitability
- Promoting descending inhibition

Opioids

	Mechanism	Medications
Full Agonist	Full μ agonist Pain control and adverse effects	Codeine Fentanyl Hydromorphone Hydrocodone Levorphanol Morphine Meperidine Methadone Oxycodone Oxymorphone
Partial Agonist	Partial μ agonist, weak κ antagonist	Buprenorphine
Mixed Agonist-Antagonist	κ agonist, μ antagonist	Nalbuphine
Antagonist	Blocks activity at μ receptor	Naloxone Naltrexone
Dual Action	μ agonist, Inhibit NE and 5-HT reuptake	Tramadol Tapentadol

Opioid analgesics are characterized by their pharmacologic differences which are derived from their complex interactions with three opioid receptors, mu (μ), kappa (κ), and delta (δ) with evidence for subtypes.

The μ receptor is the most important for analgesia

Mu1 (μ1): supraspinal analgesia, euphoria, nausea

Mu2 (μ2): urinary retention, respiratory depression, constipation, and cardiovascular side effects

Kappa (κ): spinal analgesia, dysphoria, psychomimetic effects

Delta (δ): spinal analgesia, decreased oxygen demand from brain, and cardiovascular side effects

Opioid receptors are coupled to G1 proteins. Opioids close N-type voltage-operated calcium channels and open calcium-dependent inwardly-rectifying potassium channels. This results in hyperpolarization and a reduction in neuronal excitability.

Opioids also decrease intracellular cAMP which modulates the release of nociceptive neurotransmitters (e.g. substance P).

A 4th opioid receptor has been identified but does not bind classical opioid agonists or antagonists (considered an orphan receptor).

Opioids & Pharmacogenetics

In general, drug dosing assumes patients are extensive metabolizers (EM), since these comprise the largest proportion of the population.

Absorption

- Lipophilic opioids, like fentanyl, readily cross skin and mucous membranes.
- Most opioid agonists are readily absorbed from the GI tract after oral administration.
- Bioavailability is close to 100% when an opioid is given IV.

Metabolism

The liver is the primary site of opioid metabolism.

Oral opioids are subject to significant "first-pass" metabolism:

- bioavailability of oral morphine ranges from 25-40%.
- bioavailability of oral oxycodone ranges from 60-75%.

Poor Metabolizers (PM) metabolize the target drug slowly or not at all, which increases risk of adverse effects.

PM often require lower doses of the target drug compared to EM.

Intermediate Metabolizers (IM) break down the targeted drug at a slower rate than EM

IM may require a lower dose of the target drug compared to EM

Ultra-rapid Metabolizers (UM) metabolize the target drug rapidly, resulting in decreased bioavailability and poor therapeutic response.

UM require a higher dose of the target drug compared to EM

Active metabolites may limit or prevent use, for example:

- Morphine is metabolized to morphine 3-glucuronide and morphine 6-glucuronide. These metabolites bind tightly to μ-opioid receptors. Since these active metabolites are excreted by the kidneys, they can accumulate in patients with altered renal function.
- Meperidine is metabolized to a CNS stimulant with a longer duration of action than the parent drug. Repeated use may cause seizures.

Opioid dosing

Morphine is considered the gold standard

Opioid	Equianalgesic dose		Comments
	Oral (mg)	IV (mg)	
Codeine	30 Not recommended	1.3 Not recommended	• Prodrug metabolizes to morphine. • FDA recently added CONTRAINDICATION for < 12 years of age and not recommended in pediatric patients 12-18 years of age
Morphine	**3**	**1**	• Lipophilic • Metabolized by liver to active and inactive metabolites that require renal clearance. Not recommended for renal patients • Available dosage forms: oral solution, tablet, IV, ER tablet for opioid-tolerant patients only

Ultra-rapid metabolizer
Increased CYP2D6 activity results in increased conversion to morphine

Poor or Null Metabolizer
Decreased CYP2D6 activity results in decreased conversion to morphine

Opioid dosing

Consider for patients with renal disease

Opioid	Equianalgesic dose		Comments
	Oral (mg)	IV (mg)	
Fentanyl			• Highly lipophilic • Metabolized by the liver • Very short acting 30-60 minutes • Give slow IV push, since rapid IV administration can cause chest wall rigidity that is not reversed with opioid antagonist. • Available dosage forms: IV, transmucosal, transdermal patch for opioid-tolerant patients. Transdermal plasma concentrations in patients 1.5 to 5 years of age were 2X higher than in adults
Hydromorphone	**0.75**	**0.15**	• Hydrophilic, no active metabolites • Available dosage forms: oral solution, tablet, IV, ER tablet for opioid-tolerant patients only
Hydrocodone	**3**	**NA (does not exist)**	• Metabolizes to hydromorphone • Available only as combination product with ibuprofen or acetaminophen (caution use of other medications that contain acetaminophen) • Available dosage forms: oral solution, tablet, IV, ER tablet for opioid-tolerant patients only
Levorphanol			• Metabolized by the liver, long acting • Available dosage forms: 2mg tablet, IV

Opioid dosing

Opioids in the headlines

Opioid	Equianalgesic dose		Comments
	Oral (mg)	IV (mg)	
Oxycodone	**2**	**NA (does not exist)**	• Available as single agent and in combination with acetaminophen (caution use of other medications that contain acetaminophen) • Metabolizes to oxymorphone • Available dosage forms: oral solution, tablet, ER tablet and abuse-deterrent ED tablet for opioid-tolerant patients only
Oxymorphone	**1**	**0.1**	• No active metabolites • Available dosage forms: oral solution, tablet, IV, ER tablet for opioid-tolerant patients only

Opioid dosing

Opioids for limited use

*Should only be used by experienced providers; dosage conversion dependent on the total daily dose *

Opioid	Equianalgesic dose		Comments
	Oral (mg)	IV (mg)	
Meperidine	Not recommended	Not recommended	• NOT RECOMMENDED as an analgesic since active metabolite, normeperidine, can accumulate and cause seizures
Methadone*	**1**	**0.1**	• Should only be used by experienced providers; dosage conversion dependent on total daily dose* • Active at opioid receptors and as NMDA receptor antagonist • Available dosage forms: oral liquid, tablet, IV • Inexpensive • Variable absorption (bioavailability between 50-100%) • Long acting but unpredictable half-life due to high protein binding and drug accumulation after multiple doses • Used to treat opioid use disorders every 12 to 24 hours, but analgesic for only 6-8 hours • Can prolong QTc (watch other drug interactions such as ondansetron) Monitor EKG. • Drug interactions with CYP 3A4 inhibitors and inducers

Opioid dosing

Mixed agonists-antagonist, partial agonists and dual-acting

Opioid	Equianalgesic dose		Comments
	Oral (mg)	IV (mg)	
Buprenorphine			• Partial (μ) mu-agonist and kappa (κ), antagonist, analgesic effects plateau • Use to treat pain and opioid dependence. • Available dosage forms: tablet, transmucosal, and transdermal patch for opioid tolerant patients. • Studies show shorter treatment than morphine for neonatal abstinence syndrome (NAS) when given sublingually; recommended dose is: 5.3 mcg/kg/dose every 8 hours
Nalbuphine			• (κ) Kappa-agonist, (μ) mu-antagonist • Used to treat pain and opioid induced pruritus • May be more efficacious for analgesia in woman than men
Tapentadol	**10-15**	**NA (does not exist)**	• (μ) Mu-agonist and blocks norepinephrine reuptake • Available dosage forms: tablet and extended-release tablet
Tramadol			• Blocks norepinephrine and serotonin reuptake, metabolizes to a (μ) mu-agonist • Increases risk of seizures in those with seizure disorder or in combination with other drugs that lower seizure threshold • Available dosage forms: tablet and extended-release tablet • FDA recently added CONTRAINDICATION for pediatrics because of dependence on CYP2D6 for metabolism

Opioid-related adverse effects

To treat common adverse opioid effects, use other multimodal (opioid-sparing) therapies

- Taking opioids with food does NOT decrease nausea/vomiting
- Sedation ALWAYS precedes respiratory depression
- Patients develop a tolerance to opioid-related adverse effects with continued use, except constipation

Adverse Effects	Mechanism	Management
Constipation	• Decrease intestinal secretions and peristalsis. • Most common and ONLY opioid adverse effect in which tolerance is NOT developed.	• Scheduled prophylactic bowel regimen with peristaltic laxative • Treat with peripherally acting mu-antagonists or chloride channels activator
Nausea/ Vomiting	• Common • Action on the medullary chemoreceptor trigger zone • Alteration of vestibular sensitivity	• Antiemetic (like ondansetron or scopolamine for postoperative patients >40kg)
Sedation	• Always precedes respiratory depression • Additive effects with other medications	• Titrate doses slowly • Avoid continuous infusions
Respiratory Depression	• Always preceded by sedation and predictable pattern. • Dose dependent action at the brainstem level to produce increasing respiratory depression eventually ending in apnea	• Monitor sedated patients • Titrate doses slowly • Support respiration before giving antagonist • Reversible with antagonist (naloxone, 0.01mg/kg slow IV push every 5 minutes PRN)
Pruritis, hypnogotic myoclonus	• Not an immune-mediated allergy • More common in neuraxial opioid administration and with active metabolites	• Mixed agonist-antagonist or • Low dose agonist, such as naloxone infusion
Euphoria, dysphoria, hallucinations	• Rarely reported, • Additive effects with other medications	• Change opioid
Urinary retention	• More common in males	• Monitor intake & output • Change opioids • Low dose antagonist • Catheterization

Pancreatitis, continued

Ready to wean?

What do you do now?

Patient: 3 year old female (14kg)

Pain regimen: Family chose to switch to oxycodone although the dosing interval will not be convenient. She is currently on 4mg every 4 hours

FEN: Tolerating G-tube feedings

WAT scores now 1-2 in past 24 hours

Plan is to wean by 20% every other day:

4mg → 3.2mg → 2.4mg → 1.6mg → 0.8mg → STOP

Co-analgesics and Adjuvant Analgesics

Complex Regional Pain Syndrome (CRPS)

What kind of pain does this child have?

What biobehavioral and pharmacologic interventions would you consider for this patient?

Patient: 9 year old female presents in a walking boot on LLE and ambulating with crutches. She was stepped on during a soccer game 6 weeks ago and has had ongoing burning pain since that time.

X-rays and MRI are negative.

Orthopedics recommended physical therapy and gradual return to activity. She has been unable to participate in physical therapy secondary to pain. She has not been able to wean from the boot or crutches and is unable to walk without them.

Sleep and school attendance have been significantly impacted.

Physical exam reveals trophic changes, swelling, muscle atrophy, weakness, and allodynia. She expresses extreme anticipatory fear and pain with physical exam.

Based on Budapest Criteria, she was diagnosed with CRPS.

Co-analgesics and Adjuvants

Pain is NOT the primary indication for these drug classes, but they may be helpful for pain management

Antidepressants	Used to treat chronic and neuropathic pain, may treat associated depression • SNRIs inhibit the reuptake of Serotonin (5-HT3) and norepinephrine (NE) and 5-HT3 and NE modulate descending inhibition of ascending pain pathways in brain and spinal cord. • Tricyclic antidepressants also inhibit 5-HT3 and NE, interact with GABA, block sodium channels and are alpha-1 adrenergic blockers
Anticonvulsants	Used for chronic, neuropathic, and acute postoperative pain. • Alpha-2-delta ligand calcium channel antagonists, such as gabapentin and pregablin, are currently used as first line drugs for neuropathic pain (in adults). • Other anticonvulsants used to treat pain block voltage-gated sodium and calcium channels and/or inhibit glutamate release
Steroids	Used for inflammatory pain. Due to systemic effects, use usually limited to treatment for arthritis or metastatic bone pain
NMDA receptor antagonists	Used as a general anesthetic and has potential benefit at lower doses for depression and neuropathic pain, i.e., ketamine.
Alpha$_2$-Adrenergic agonists	Used to treat hypertension, can inhibit nerve conduction, i.e. clonidine Available dosage forms: oral solution, tablet, transdermal patch and epidural administration

Co-analgesics and Adjuvants

Local anesthetics	• Used to treat acute and neuropathic pain by blocking sodium channels to inhibit the production of action potentials along the nociceptive afferent and interfere with propagation of action potentials along the nerve, at the dorsal root ganglion and along the spinothalamic tracts. • Available dosage forms: oral solution, topical eutectic or liposomal mixture, transdermal patch, IV, and epidural administration
Muscle relaxants and anxiolytics	• Used to relax skeletal muscle, treat muscle spasm and pain associated anxiety • Mechanism of action involves modulation of GABA at presynaptic receptors in dorsal horn and brainstem, but for most dugs is unknown and may be limited to sedation or anxiolysis, i.e. baclofen, diazepam, methocarbamol
Antispasmotics	• Used to treat abdominal or bladder spasms and cramping. • Anticholinergic effects, i.e. dicyclomine, hyoscyamine, and oxybutynin.
Capsaicin	• Used to treat neuropathic pain. • This active component of chili peppers is a transient receptor potential vanilloid 1 receptor agonist (TRPV1) that desensitizes pain transmission and depletes substance P.
Cannabis	Used to treat chemotherapy induced nausea and now legal in over half of US states for medicinal use by adults. • Mechanism of action may be related to Cannabidiol (CBD) effect on cannabinoid receptors or psychoactive effects from tetrahydrocanabinol (THC), but limited pain relief reported from synthetic THC products, like Dronabinol. • NOT recommended for treating pediatric patients due to potential long-term neurodevelopmental effects.

In Summary…

Key Points

"Cure sometimes, treat often, comfort always." ~Hippocrates

Since medications are dosed based on weight, a tablet or capsule is not "one size fits all".

Key assessments for developing a child's pain treatment plan:

- Past/current pain control methods and their effectiveness
- Multiple sites, causes, and types of pain
- Comprehensive medication and pain treatment history
- Drug-related fears

Treat pain based on cause, type, site, and severity

- Develop realistic treatment goals
- Develop an age and developmentally-appropriate multi-modal pain treatment plan

Implement pain treatment plan

- Give adequate doses at appropriate intervals (duration of analgesia)
- Reassess pain regularly and document assessment
- Evaluate treatment efficacy and document evaluation
- Pharmacological treatment for pediatric patients are dosed by weight, age, and sometimes body surface area

Dosing

- Many medications have not been studied in pediatric patients and dosing may be empirical or extrapolated from adult doses
- Adjust medications based on individual patient response and adverse effects.

Pharmacologic options

- The mainstays of analgesia are non-opioids and opioids.
- However, there are many other medications commonly included in treatment plans to treat pain, associated symptoms and conditions, and analgesic adverse effects
- These medications may or may not have analgesia as a primary treatment indication.
- Non-opioids include acetaminophen and NSAIDs.
- In the opioid category, morphine is the prototype.
- Co-analgesics or adjuvant analgesics include local anesthetics, antidepressants and anti-seizure drugs.

Evaluate & monitor effectiveness of the treatment plan

- How would you rate your ability to recommend pharmacologic pain treatments for children?
- What resources do you need to review with your team?
- What is your next step?

Appendix

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