



Pediatric Pain Management

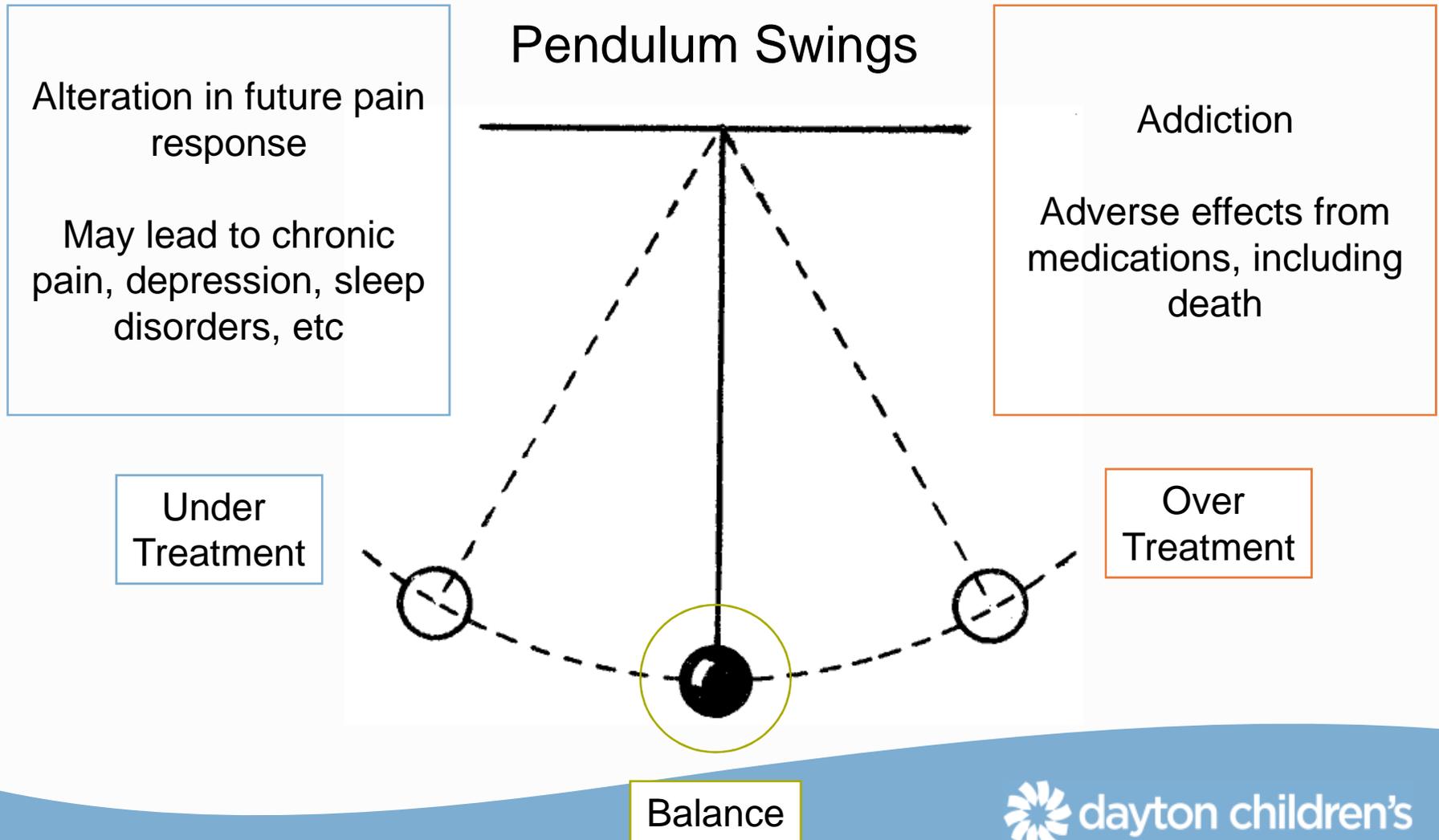
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Objectives

1. Identify current challenges in managing pediatric pain
2. Review the pathophysiology and classification of pain
3. Describe a stepwise approach for managing pediatric pain
4. Discuss the pharmacologic properties such as mechanism of action, typically dosing, and adverse effects of each therapeutic modality used to prevent and/or treat acute pediatric pain

Background



Background

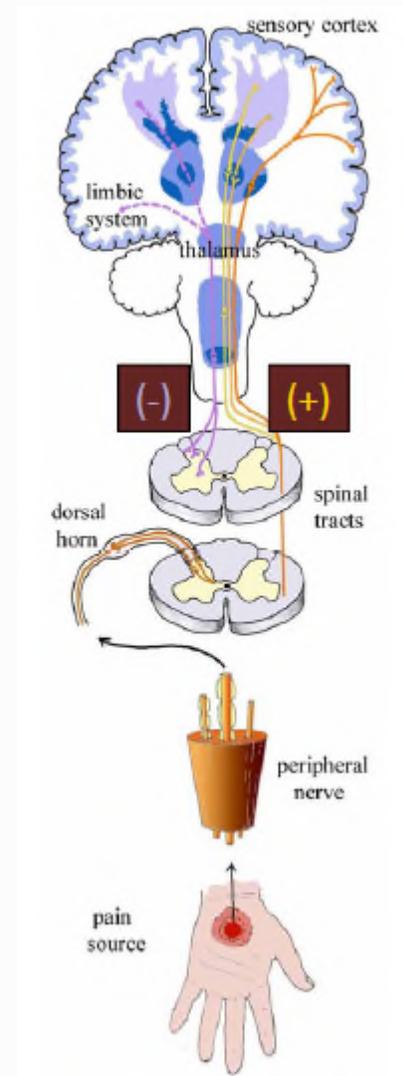
Four most commonly used pain classification systems

- 1) Mechanism (nociceptive, neuropathic, functional)
- 2) Duration (acute, chronic, breakthrough)
- 3) Etiology (malignant, non-malignant)
- 4) Anatomical location

Background

Pathophysiological Mechanisms of Pain

- Nociceptive
 - Somatic
 - From skin, bone, joint, muscle or connective tissue
 - Well localized
 - Sharp, aching, squeezing, stabbing, or throbbing
 - Visceral
 - From internal organs
 - Referred pain
 - Dull, crampy, or achy
- Neuropathic – arising from nerve damage
 - Burning, shooting, electric, tingling
- Functional – Abnormal operation of nervous system



Background

Duration of Pain

- Acute pain
 - Sudden onset felt immediately following injury, often severe in intensity but usually short-lasting
 - Protective physiological response
 - Usually nociceptive
 - Can result in chronic pain if left untreated
- Chronic pain
 - Continuous or recurrent pain that persists beyond the expected normal time of healing
 - Can negatively affect all aspects of daily life
 - Nociceptive, neuropathic, functional, or mixed
- Episodic or recurrent
- Breakthrough pain

Treatment Approach

Principles of Pain Management

- Prevent pain
- Accurate assessment of the child's pain is key
- Address and treat the cause of pain
- Incorporate non-pharmacologic methods
- Match analgesic choice to type of severity of pain
- Titrate to response
 - Lowest effective dose by the simplest route
 - Minimize side effects
 - Reassess and adjust medications at regular intervals and as necessary
- Consider adjuvant medications if appropriate
- Referral to a pain specialist or palliative care team can be helpful in managing patients with pain that is chronic and/or difficult to control

Pediatric Pain Assessment

- Non-verbal or cognitive impairment
 - Neonatal Infant Pain Scale (NIPS)
 - Neonatal Pain Assessment and Sedation Scale (N-PASS)
 - Revised Faces, Legs, Activity, Cry, and Consolability (r-FLACC)
- Verbal, alert and oriented
 - Wong Baker Faces
 - Numerical Rating Scale
 - Visual Analogue Scale
 - Verbal Numeric Scale



Categories ▼	Score Zero ▼	Score One ▼	Score Two ▼
Face F	No particular expression or smile	Ocasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs L	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity A	Lying quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry C	No crying (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability C	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distactable	Difficult to console or comfort

Treatment Modalities

- Prevention
- Non-pharmacologic treatments
- Pharmacologic preventions and treatments
 - Oral sucrose
 - Topical and local anesthetics
 - Non-opioid
 - Opioids

Prevention

- Minimize frequency of blood sampling
- Cluster cares / procedures whenever appropriate / feasible
- Avoid or minimize painful routes of medication administration (i.e. IM, rectal, etc)

Non-Pharmacologic Treatments

- Should be considered with all pain management
- Non-pharmacologic pain management may decrease:
 - Time of recovery for procedures
 - Use of opioids and/or anxiolytics
 - Decrease adverse events
- Techniques include:
 - Conversation and therapeutic language
 - Coaching and preparation
 - Psychological and cognitive behavioral interventions
 - Physical / sensory Interventions

Pharmacologic Treatments

WHO's principles for the pharmacological management of pain

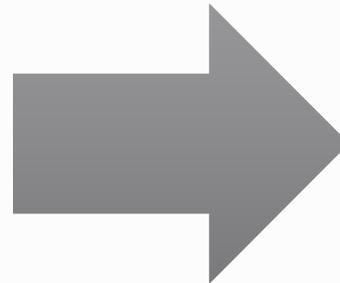
- Use a two-step strategy
- Dose at regular intervals
- Use the appropriate route of administration
- Adapt treatment to the individual child

Pharmacologic Treatments

Two-Step Strategy

Step 1: Mild Pain

Non-opioids



Step 2: Moderate to Severe Pain

Opioids
(± non-opioids)

Oral Sucrose [Pharmacologic Treatments]

Indication:

- Infants < 6 months
- Prophylaxis prior to
 - Minor procedures (ex. Heel sticks, Foley catheter insertion, eye exams, etc)
 - Immunization administration

Mechanism of Action: Unknown

Dose and administration:

- 0.1 – 2 mL of 24% sucrose based on gestational age
- 2 minutes prior to painful stimuli
- Dipping pacifier and allowing non-nutritive sucking may be more effective

Duration: 3 – 5 minutes

Limit: <10 doses/day

Topical Anesthetics [Pharmacologic Treatments]

Indication:

- Variety of minor procedures and repairs (Venipuncture, IM medication administration, lumbar puncture, oral inflammation, etc)
- Note: not approved for relief of teething pain

Mechanism of Action: Blocks both the initiation and conduction of nerve impulses

General notes:

- Limit area of application for infants and young children due to increased BSA and risk of toxicity
- Avoid use of prilocaine containing products in:
 - Neonates
 - Children with methemoglobinemia
 - Infants with predisposition to methemoglobinemia (G6PD deficiency, etc)

Topical Anesthetics [Pharmacologic Treatments]

Commonly used agents in pediatrics

Agent	Dose	Max Dose	Onset / Duration	Notes
LMX4 Liposomal lidocaine 4%	< 4 YO: 1 g ≥ 4 YO: 1 – 2.5 g Apply to puncture area (6.25 cm ² of skin)	3 – 4 times per day (4.5 mg/kg/day)	Onset: 30 minutes Duration: 60 minutes	Available over-the-counter
EMLA Lidocaine 2.5% + Prilocaine 2.5%	< 5 kg: ≤ 1 g/10 cm ² area ≥ 5 kg: 1 – 2 g/10 cm ² area	Maximum total dose / area: < 5kg : 1g / 10 cm ² 5 – 10 kg: 2 g / 20 cm ² 10 – 20 kg: 10 g / 100 cm ² >20 kg: 20 g / 200 cm ²	Onset: 60 minutes Duration 3 - 4 hours	Risk of methemoglobinemia

Topical Anesthetics [Pharmacologic Treatments]

Commonly used agents in pediatrics (cont.)

Agent	Dose	Max Dose	Onset / Duration	Notes
Synera patch Lidocaine 70 mg + Tetracaine 70 mg	≥ 3 YO: Apply to area 20 – 30 minutes prior to procedure	Simultaneous or sequential application of multiple patches is not recommended	Onset: 20 – 30 minutes Duration: 90 minutes	<ul style="list-style-type: none"> • Use immediately after opening pouch • Do not cut or remove the top cover • Fold adhesive together following use
Pain Ease Vapocoolant spray	Spray long enough to cause skin blanching but not freezing (4 – 10 seconds)	When skin turns white (freezing)	Onset: Immediate Duration: a few seconds	Freezing may alter skin pigmentation

Local Anesthetics [Pharmacologic Treatments]

Indications: Variety of minor procedures (abscess drainage, vascular access procedure, lumbar puncture, etc)

Mechanism of Action: Blocks both the initiation and conduction of nerve impulses

Often includes option of with or without epinephrine

Role of epinephrine:

- 1) Increases the duration of action
- 2) Decreases local bleeding during procedure
- 3) Reduces systemic absorption of anesthetics

Local Anesthetics [Pharmacologic Treatments]

		Potency	Onset of Action	Duration of action	Maximum dose*
Lidocaine	Without epinephrine	2	Rapid (≤ 2 mins)	0.5 – 2 hrs	5 mg/kg
	With epinephrine			1 – 3 hrs	7 mg/kg
Bupivacaine	Without epinephrine	4	Slow (> 5 mins)	2 – 4 hrs	2.5 mg/kg
	With epinephrine			4 – 8 hrs	3 mg/kg
Mepivacaine	Without epinephrine	1	Medium (3 – 5 mins)	2 – 3 hrs	5 mg/kg
	With epinephrine			2 – 6 hrs	7 mg/kg

*Published maximums. However, for added margin of safety, **reduce maximum allowable dose** in children < 8 YO to 80% and further for neonates and infants due to risk of increased free fraction of local anesthetic leading to toxicity

Local Anesthetics [Pharmacologic Treatments]

J-tip applicator – Needle-free Injection System

- Uses compressed carbon dioxide to administer liquid lidocaine through the skin into the subcutaneous tissue
- Recommended to use with Buffered 1% lidocaine or preservative-free lidocaine
- Onset: 1 – 2 minutes
- Duration: 15 – 30 minutes



Local Anesthetics [Pharmacologic Treatments]

Contraindication:

- Large or multiple laceration that may require doses above maximum allowable

Avoid epinephrine use:

- Consider avoiding use in areas that have an end arterial supply such as digits and penial due to risk of ischemia
- Comorbidities such as severe hypertension, coronary artery disease
- Catecholamine sensitivity

Adverse effects

- Injection site pain: May be reduced by buffering with sodium bicarbonate and warming to room temperature
- Systemic toxicity (CNS and cardiovascular)
 - Manage symptoms
 - Lipid therapy (1-3 ml/kg bolus)

Acetaminophen [Pharmacologic Treatments]

- Indication
 - Mild pain
 - Moderate to severe pain in conjunction with opioids
- Mechanism: Inhibit the synthesis of prostaglandins in the CNS and work peripherally to block impulse generation
- Dosing
 - Typical dosing: 7.5 to 15 mg/kg every 4 to 6 hours
 - Maximum dosing
 - Neonates: 22.5 – 75 mg/kg/day (depending on post-menstrual age)
 - Pediatrics: 75 mg/kg/day, not to exceed 4000 mg/day
 - Adolescents / Adults: 4000 mg/day
 - Remember to check if the patient is getting acetaminophen from other sources
 - Impairments:
 - Renal: Consider decreasing daily dose and extending dosing interval
 - Hepatic: Use with caution. Avoid chronic use in hepatic impairment

Acetaminophen [Pharmacologic Treatments]

Available formulations

- Oral solution / suspension
 - Infant concentrated drops 80 mg/0.8 mL have been taken off the market
- Oral tablets / capsules
- Chewable tablets
- Oral disintegrating tablets
- Rectal suppositories
- Intravenous solution
 - Cost per 1000 mg
 - \$52 (IV) vs \$0.20 (tabs) vs \$0.63 (liquid)



Acetaminophen [Pharmacologic Treatments]

- Contraindications

- Severe hepatic impairment or severe active liver disease

- Warnings

- BBW: Associated with acute liver failure, at times resulting in liver transplant and death

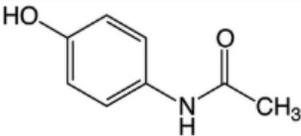
- Skin reactions (rare)

- Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) has occurred rarely

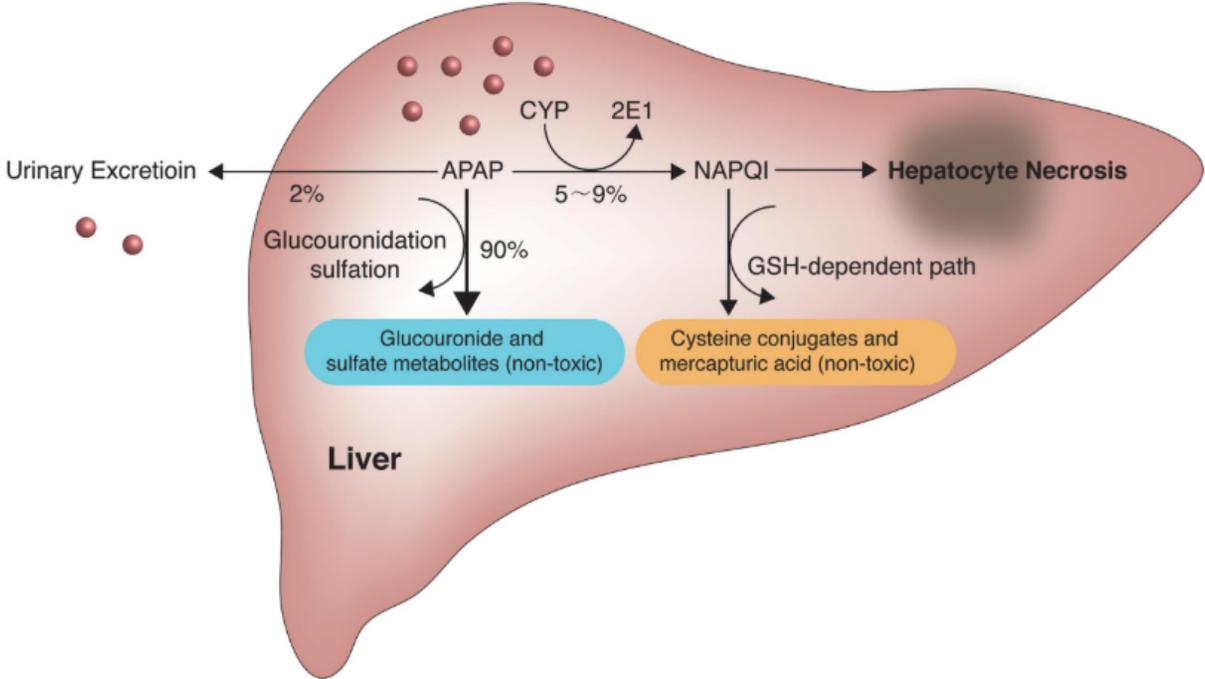
- Avoid prophylactic use to reduce fever and discomfort associated with vaccinations

- Decreases the immune response of some vaccines
- Antipyretics may be use to treat fever or discomfort following vaccination

Acetaminophen [Pharmacologic Treatments]



Acetaminophen (APAP, Paracetamol) ●



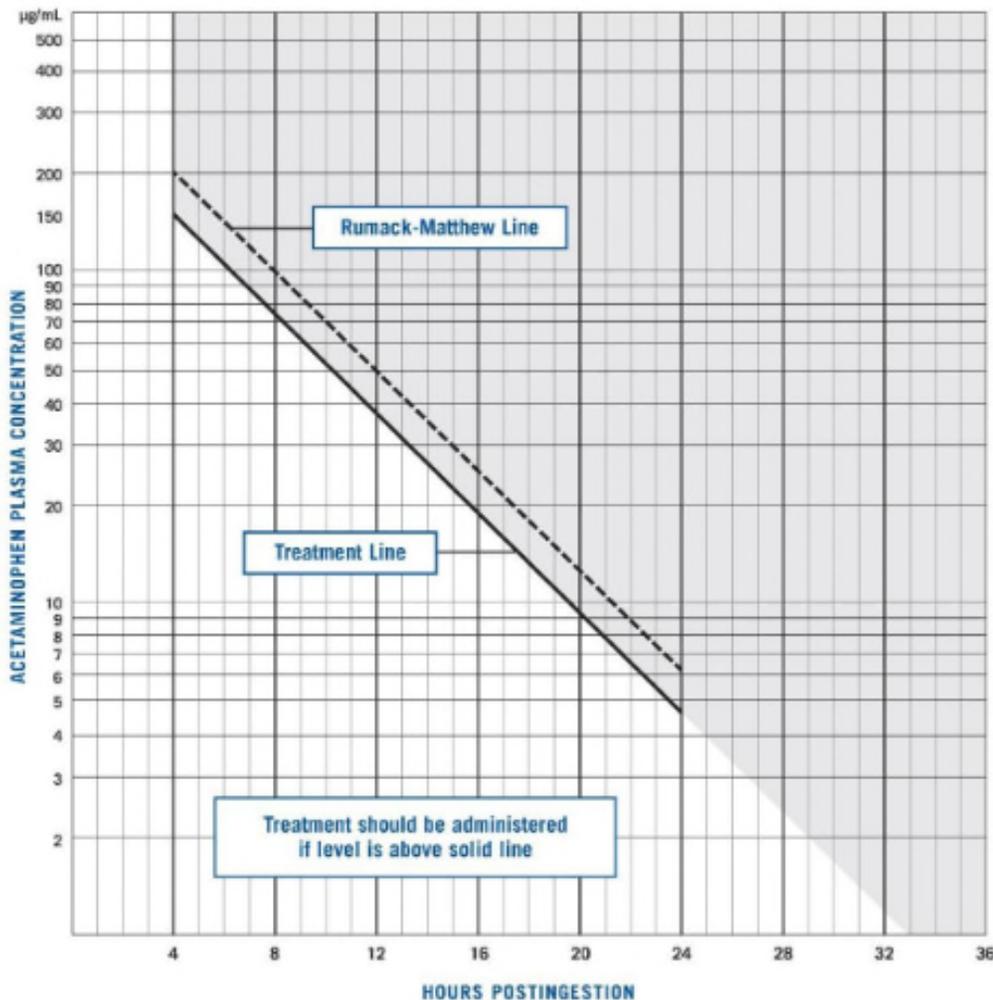
Acetaminophen [Pharmacologic Treatments]

Require hospital management

- Acute ingestions
 - At once or over 24 hour period
 - ≥ 200 mg/kg or 10 g (which ever is lower)
- Chronic ingestions
 - 48 hours or more
 - 150 mg/kg/day or 6 g/day x 2 days (which ever is lower)
- Amount unknown

Call **POISON CONTROL** to
speak to an expert
1-800-222-1222

Acetaminophen [Pharmacologic Treatments]



Obtain a 4 hour concentration

If treatment is needed, N-acetylcysteine (NAC) should be initiated within 8-10 hours of ingestion

Continue until acetaminophen concentrations are undetectable and LFTs are downtrending

Minimum duration:

- IV: 21 hours
- Oral: 72 hours

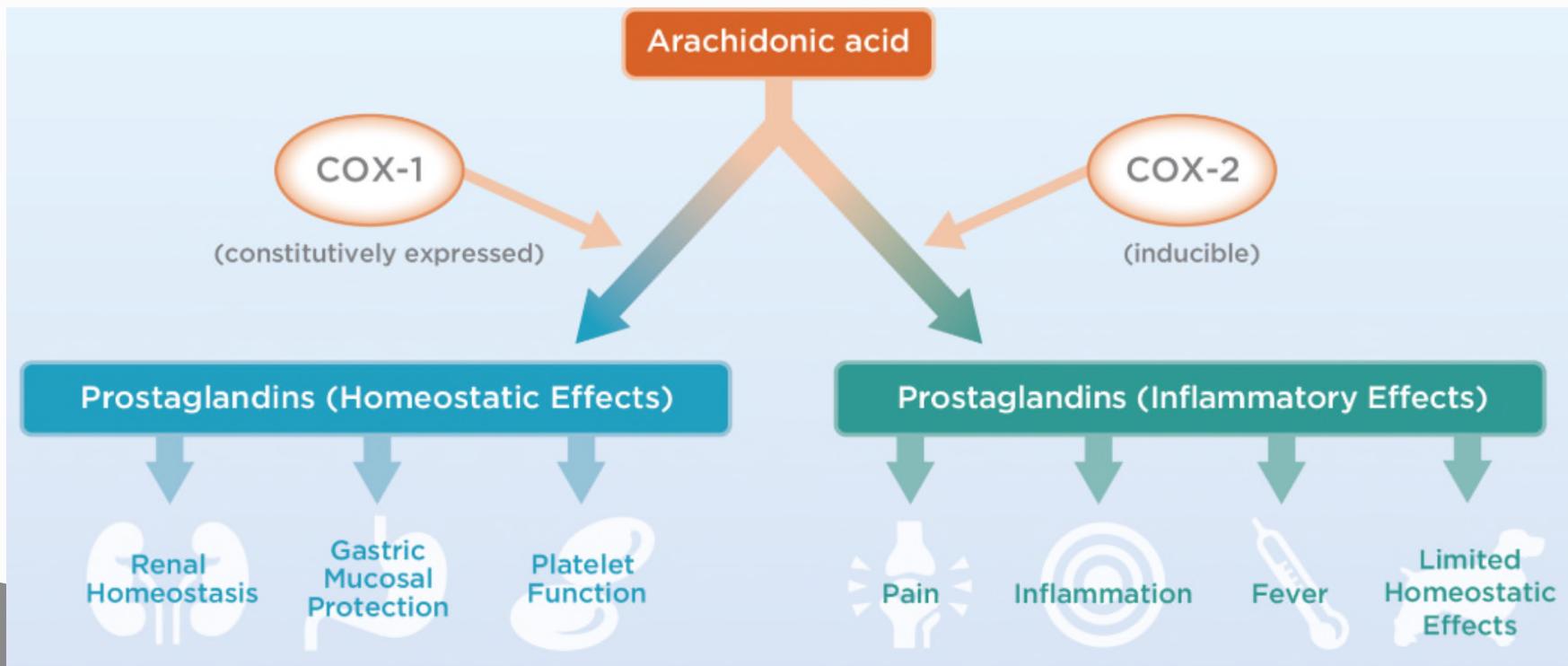
Notes of oral administration:

To best mask sulfur odor – dilute with cola, ice cold, with lid, through straw

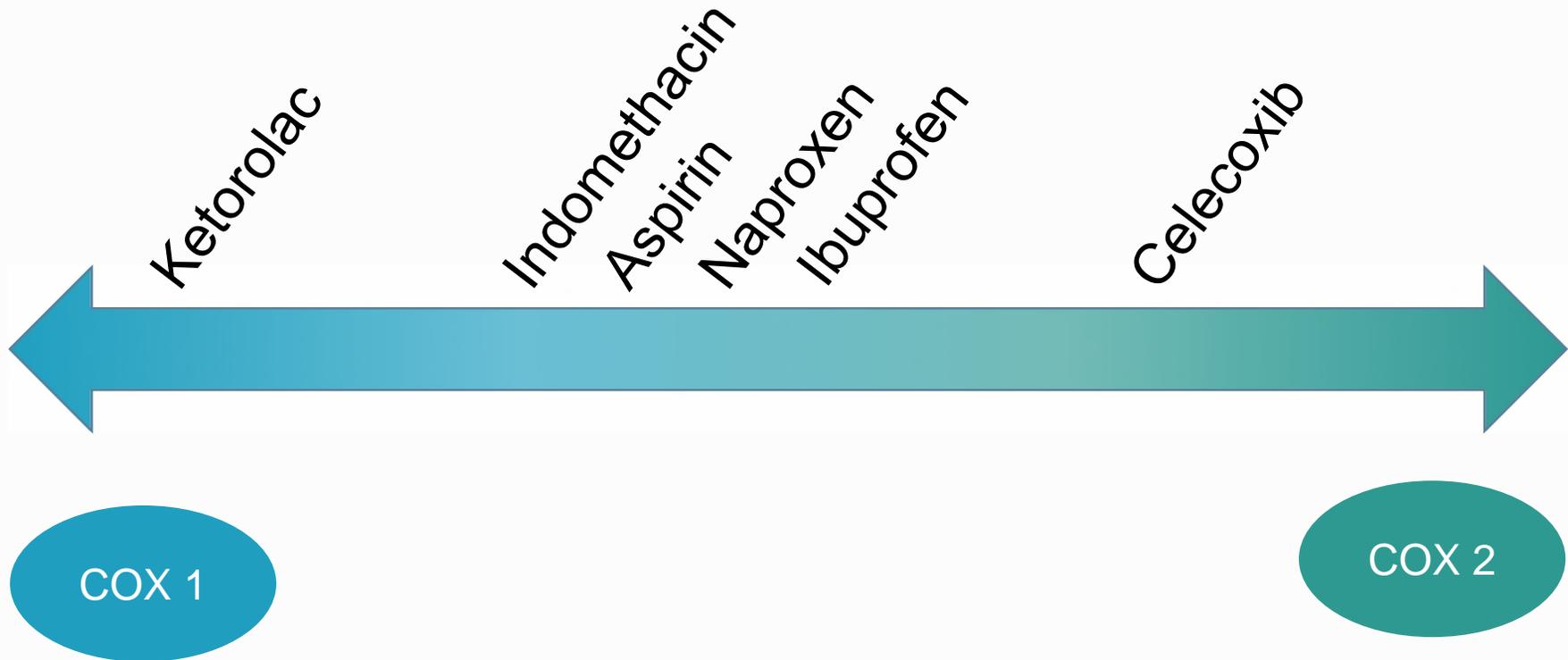
NSAIDS [Pharmacologic Treatments]

- Indication

- Mild pain
- Moderate to severe pain in conjunction with opioids
- Inflammatory pain



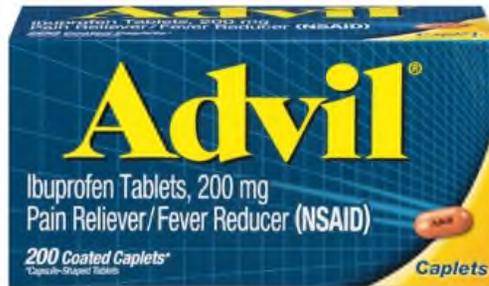
NSAIDS [Pharmacologic Treatments]



NSAIDS [Pharmacologic Treatments]

	Ibuprofen (Motrin ®, Advil ®, Caldolor ®)	Naproxen (Naprosyn ®, Aleve ®)	Ketorolac (Toradol ®)
Dosing	4 – 10 mg/kg Every 6 – 8 hours	5 mg/kg Every 12 hours	0.5 mg/kg Every 6 – 8 hours
Max dose	40 mg/kg/day 2,400 mg/day	1000 mg/day (OTC labeling: 600 mg/day)	IV/IM: <50 kg :60 mg/day ≥ 50 kg: 120 mg/day PO: 40 mg/day
Renal dosing	KDIGO 2012 guidelines on NSAIDs: eGFR 30 – 60: Avoid use with concurrent disease that increases risk of AKI eGFR <30: Avoid use		
Hepatic dosing	No adjustments		
Special Considerations	Avoid use <6 months of age	OTC labeling ≥ 12 YO	**Max duration: < 2YO: 2 to 3 days ≥2 YO: 5 days

NSAIDS [Pharmacologic Treatments]



NSAIDS [Pharmacologic Treatments]



50 mg per 1.25 mL



100 mg per 5 mL (teaspoon)

NSAIDS [Pharmacologic Treatments]



NSAIDS [Pharmacologic Treatments]

Note: Dosing is based on naproxen base

200 mg
Naproxen
(base)

=

220 mg
Naproxen
Sodium



NSAIDS [Pharmacologic Treatments]



NSAIDS [Pharmacologic Treatments]

- **Contraindications**

- Use in the setting of coronary artery bypass graft (CABG) surgery

- **Warnings**

- Gastrointestinal events (BBW)

- Include gastric and/or duodenal ulcers, perforations, gastric outlet obstructions, and bleeding
- Risk increases with history of complicated ulcer, use of multiple NSAIDs, high-dose NSAID, use of anticoagulant, use of corticosteroids

- Cardiovascular events (BBW)

- May cause fatal MI and stroke

- Pregnancy: Avoid use starting at 30 weeks gestation (due to risk of premature PDA closure)

- Avoid use in volume depleted patients due to increased risk of AKI

- Avoid use with history of aspirin or NSAID exacerbated asthma

NSAIDS [Pharmacologic Treatments]

- Aspirin

- Pharmacologic effects are dose dependent

- Low dose → antiplatelet aggregation
 - Moderate dose → analgesic, antipyretic
 - High dose → anti-inflammatory

- Warnings

- Reye's syndrome

- Risk increases with history of or concomitant viral infection or with live attenuated vaccines
 - Monitor for behavioral changes, nausea, vomiting → early signs of Reye's syndrome

- Aspirin exacerbated asthma

- COX 1 inhibition → increased production of leukotriene → bronchoconstriction

NSAIDS [Pharmacologic Treatments]

- Aspirin

- Pharmacologic effects are dose dependent

- Low dose → antiplatelet aggregation
 - Moderate dose → analgesic
 - High dose → anti-inflammatory

- Warning

**AVOID USE
FOR PAIN MANAGEMENT**

- Avoid use in children with viral infection or with live/attenuated vaccines
 - Symptoms: fever, rash, diarrhea, nausea, vomiting → early signs of Reye's

- Avoid use in children with asthma

- Mechanism: inhibition → increased production of leukotriene → bronchoconstriction

Post-operative Multi-modal Opioid-Sparing Approach

- Local anesthesia whenever feasible
- Alternate acetaminophen and NSAID around the clock
 - Duration should be tailored to:
 - Anticipated pain level and duration
 - Risk of side effects (i.e. AKI, bleeding, etc)
- Lowest effective dose of opioids
 - Moderate pain: PRN
 - Severe pain: Around the clock

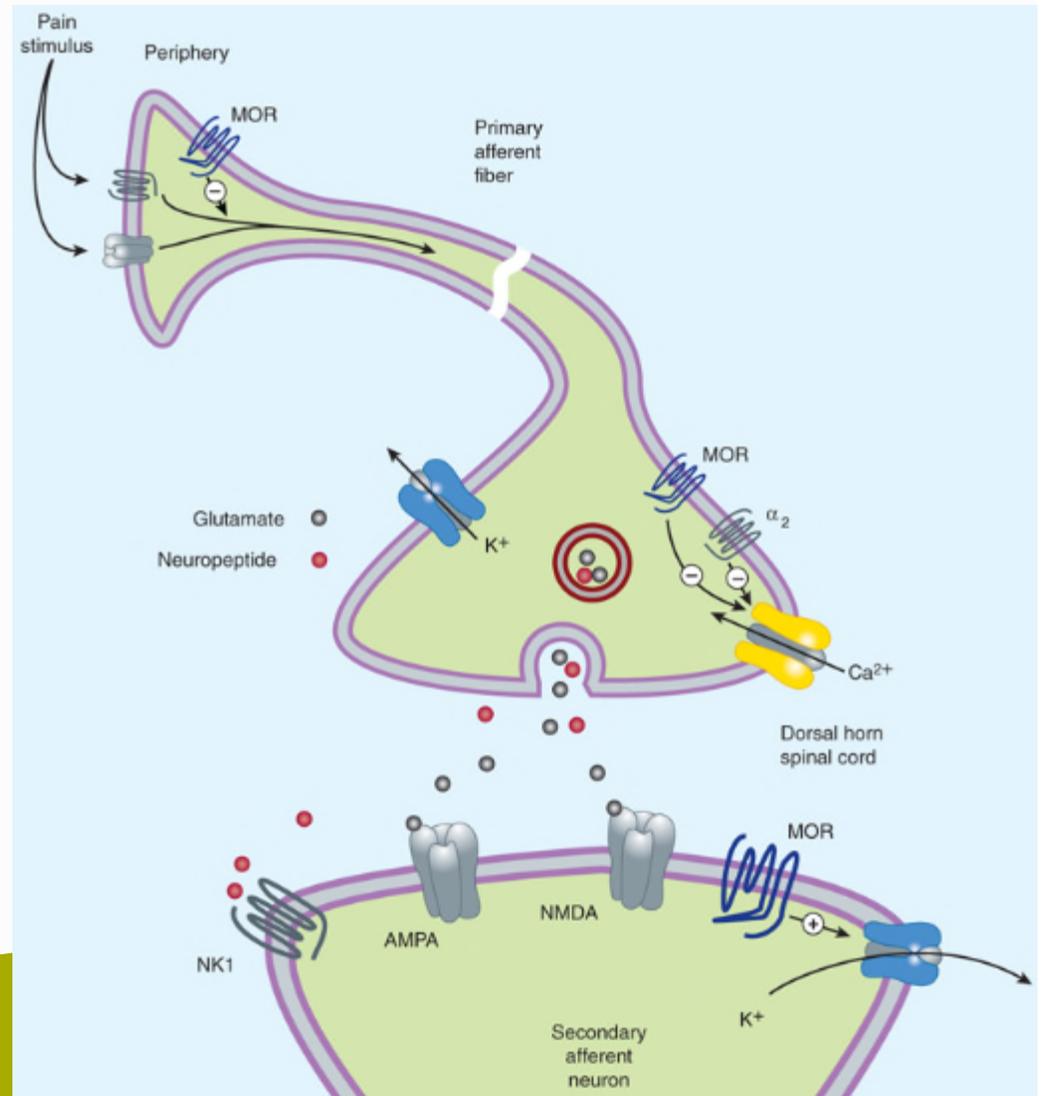
Opioids [Pharmacologic Treatments]

General Indication

- Moderate to severe pain
- Management of pain unresponsive to non-opioid analgesics

Mechanism of Action

- Opioid agonists produce analgesia by binding to opioid receptors located in the brain and spinal cord regions involved in the transmission and modulation of pain



Opioids [Pharmacologic Treatments]

Opioid receptor subtypes	Function
μ (mu)	<ul style="list-style-type: none">• Supraspinal and spinal analgesia• Sedation• Inhibition of respiration• Slowed GI transit• Modulation of hormone and neurotransmitter release
δ (delta)	<ul style="list-style-type: none">• Supraspinal and spinal analgesia• Modulation of hormone and neurotransmitter release
κ (kappa)	<ul style="list-style-type: none">• Supraspinal and spinal analgesia• Psychotomimetic effects• Slowed GI transit

Opioids [Pharmacologic Treatments]

	Chemical Source	Receptor Effects			Histamine Release
		μ	δ	κ	
Phenanthrenes (morphine-like agonists)					
Morphine	Natural	+++		+	+++
Hydromorphone	Semisynthetic	+++			+
Hydrocodone	Semisynthetic	\pm			N/A
Oxycodone	Semisynthetic	\pm			+
Phenylpiperidines (meperidine-like agonists)					
Fentanyl	Synthetic	+++			+
Diphenylheptanes (methadone-like agonists)					
Methadone**	Synthetic	+++			+
Agonist-antagonist derivatives					
Buprenorphine	Synthetic	\pm	--	--	N/A

42 **Note: not a comprehensive list of agents

Opioids [Pharmacologic Treatments]

	Starting dose	Equianalgesic dose	
		PO	IV
Morphine	PO: 0.1 – 0.2 mg/kg every 2-4 hr IV: 0.05 – 0.1 mg/kg every 2-4 hr	30 mg	10 mg
Hydromorphone	PO: 0.03 mg/kg every 4-6 hr IV: 0.015 mg/kg every 4-6 hr	7.5 mg	1.5 mg
Hydrocodone	PO: 0.1 – 0.2 mg/kg every 4-6 hr	30 mg	--
Oxycodone	PO: 0.1 – 0.2 mg/kg every 4-6 hr	20 mg	--
Fentanyl	IV: 0.5 – 1 mcg/kg every 1-2 hr	--	0.1 mg (100 mcg)
Methadone	PO: 0.1 mg/kg every 6-8 hr IV: 0.05 – 0.1 mg/kg every 6-8 hr	Variable	Variable

- Dosing for infants >6 months old
- For obese patients, starting dose should be based on ideal body weight
- PO dosing is based on immediate release formulation

Opioids_[Pharmacologic Treatments]

General rules for titrating opioids

- Allow medication to reach steady state (3 – 5 half-lives, typically 24 – 48 hours) before considering to titrate up
- Increase by 10 – 20 %
- Allow medication to reach steady state after each titration
- Monitor for dose limiting adverse effects (i.e. respiratory depression)

Opioids_[Pharmacologic Treatments]

Contraindications

Tramadol and **codeine** are contraindicated in:

- All children < 12 YO
- Children of all ages that had tonsillectomy and/or adenoidectomy

Use should be cautioned in children \geq 12 YO with:

- Obesity
- Obstructive sleep apnea
- Severe lung disease

Due to variability in metabolism in children that can alter the level of active drug, resulting in life-threatening respiratory depression

Opioids [Pharmacologic Treatments]

Warnings – Fatal respiratory depression

- As dose of opioids are increased, the respiratory center becomes less responsive to CO₂ → progressive respiratory depression
- Often manifests as decrease in respiratory rate
- Increased risk with:
 - Underlying pulmonary dysfunction
 - Head trauma patients who are not ventilated
 - Patients with renal dysfunction
 - Through excess accumulation of M3G metabolite

Opioids [Pharmacologic Treatments]

Naloxone (Narcan ®)

- Pure opioid antagonist that compete and displaces opioids at receptor sites
- Full opioid reversal
 - IV/IM: 0.1 mg/kg/dose (max 2 mg/dose)
 - Intranasal:
 - Narcan nasal spray: 4 mg/dose
 - Parenteral formulation (≥ 13 YO): 2 mg (1 mg/nostril)
- Partial opioid reversal
 - IV/IM: 0.001 mg/kg/dose (1 mcg/kg)
- Repeated every 2-3 minutes as needed



Opioids [Pharmacologic Treatments]

Adverse effects – Constipation

- Opioid receptors exist in high density in the GI tract
- When opioids bind to these receptors → reduces peristalsis → increased transit time → excessive water and electrolyte reabsorption → constipation
- Prophylaxis / Treatment strategies
 - Increase fluid intake and dietary fiber
 - Glycerin supps for infants
 - Miralax for children and adolescents
 - Senna + docusate
- If refractory to above strategies, use of opioid antagonists may be considered

Opioids [Pharmacologic Treatments]

Adverse effects – Others

- Sedation
- Euphoria
- Nausea and vomiting
- Pruritus
- Urinary retention
- Bradycardia
- Hypotension
- Chest wall rigidity (fentanyl)
- QT prolongation (methadone)

Opioids [Pharmacologic Treatments]

Tolerance

- Tolerance is the reduction of drug effect over time as a result of exposure to the drug
- Generally does not clinically manifest until after 2 – 3 weeks of frequent exposure
- Develops more rapidly when large doses are given at short intervals
- Degree of tolerance

High	Moderate	Minimal or none
Analgesia	Bradycardia	Constipation
Euphoria, dysphoria		Miosis
Sedation		Convulsion
Respiratory depression		
Urinary retention		
Nausea and Vomiting		

Opioids [Pharmacologic Treatments]

Withdrawal or abstinence syndrome

- Onset and duration is dependent on the half-life of the opioid
 - Short-acting (morphine, fentanyl, oxycodone, etc)
 - Onset: within 6 – 12 hours
 - Duration: several days
 - Long-acting (methadone)
 - Onset: 24 – 48 hours
 - Duration: couple weeks
- Severity is usually dependent on duration and dosage of opioid use
- Signs and symptoms
 - Early stage: Anxiety, insomnia, diaphoresis, stomach cramps
 - Late stage: Tachycardia, hypertension, tremors, muscle cramps, vomiting, diarrhea, seizures
- Prevention = weaning
 - Empirically: 10 – 20% every 24 – 48 hours
 - Consider switching to methadone
 - Monitor s/s of withdrawal (WAT-1 scoring)
 - Patient specific



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