

Pediatric Pharmacotherapy 101: Pain Management

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Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.
 - This discussion will include the use of medications for off-label indications.
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Objectives

- Identify barriers to effective pain management in pediatric patients
 - Describe age-appropriate non-pharmacological pain management techniques
 - Evaluate pharmacological treatment options for managing pain in children
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Patient Case: Canter

12 year-old male awaiting cardiac transplant

- Listed IB for transplant (failed Fontan) on ambulatory milrinone
 - Recently discharged from the hospital after prolonged course now being followed by palliative care
 - Weight: 24 kg Height: 127 cm
 - Lives at home; Mom is primary caregiver
 - PMH:
 - Complete AV canal and total anomalous pulmonary venous return connection status post Fontan
 - Failing physiology with ventricular dysfunction
 - History of thromboembolism
 - CC:
 - Increasing side/back/abdominal pain and headaches
 - Slow decline of appetite and energy since initial transplant evaluation/listing
 - Allergy: NKDA
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Patient Case: Canter

12 year-old male awaiting cardiac transplant

- **Clinical Pearl: Congenital Heart Disease**

- Complete AV canal and total anomalous pulmonary venous return connection
- Failing physiology with ventricular dysfunction

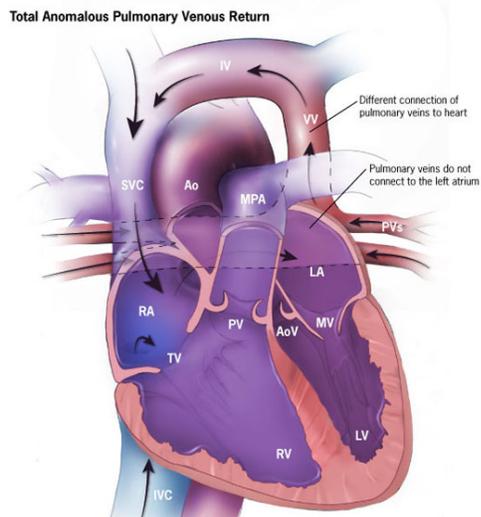


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Patient Case: Canter

12 year-old male awaiting cardiac transplant

Medications	Directions
acetaminophen (Tylenol®)	325 mg po q6hrs <i>13.5 mg/kg/dose</i>
amoxicillin	250 mg po BID
famotidine (Pepcid®)	20 mg po daily
furosemide (Lasix®)	40 mg po BID <i>1.7 mg/kg/dose</i>
milrinone	0.5 mcg/kg/min IV continuous infusion <i>via PICC line</i>
spironolactone/ hydrochlorothiazide (Aldactazine®)	25 mg po daily <i>~1 mg/kg/dose</i>
warfarin (Coumadin®)	3 mg po daily

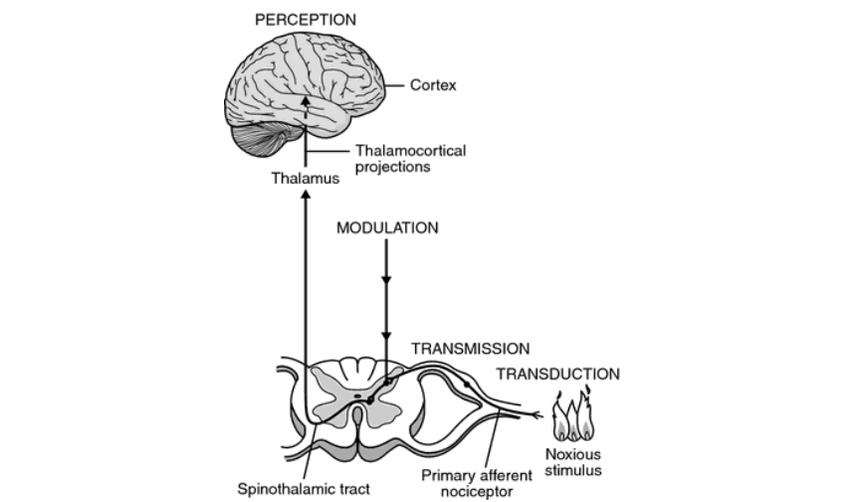
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Barriers to Effective Pain Management

Common Pain Myths

- Young infants do not feel pain
- Children tolerate pain better than adults
- Children become easily addicted to opioids
- Children are not able to tell you where they hurt
- Children become accustomed to pain
- Children will tell you when they have pain
- Children's behavior reflects their pain intensity

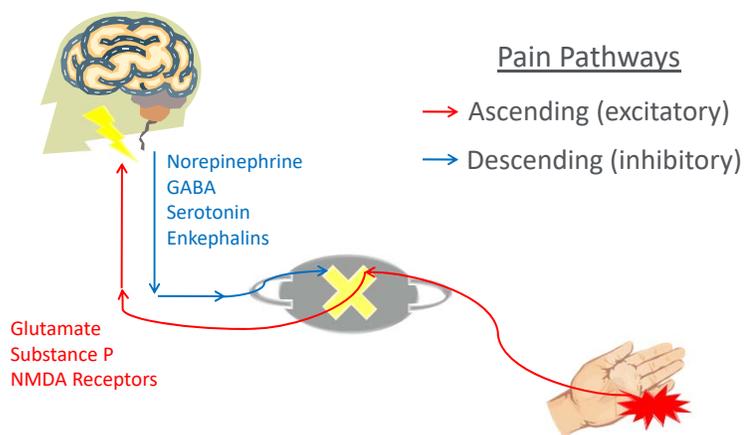
Nociception



<http://medical-dictionary.thefreedictionary.com/nociperception>

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Pain Pathophysiology



Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd Ed. Sunderland: Sinauer Associates; 2001. Central Pain Pathways: The Spinothalamic Tract.

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Barriers to Pain Relief

Challenges

- Subjective
- No single cure
- Assessment/re-evaluation process
- Multiple causes/ effects

Parents/ Caregiver

- Fear of giving up
- Opioids "too strong"
- Fear of side effects
- Concern of addiction
- Cultural or religious beliefs

Healthcare Providers

- Inadequate knowledge & training
- Misconceptions of side effects
- Opioids may shorten life expectancy
- Concern of tolerance

Concerns

- Tolerance
- Dependence
- Addiction



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Pain Terminology

Tolerance	Loss of effect of a pharmacological agent over a prolonged period of use, or the need to escalate the dose of the agent to maintain the same pharmacological effect
Dependence	State of adaptation manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, and/or administration of an antagonist
Addiction	Primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations; Compulsive desire to use the drug despite harm

Consequences of Untreated Pain

Physical	<ul style="list-style-type: none">• Release stress corticosteroids• Poor appetite, decreased bowel function• Altered sleep• Fatigue/ decreased activity• Compromised immune system
Psychosocial	<ul style="list-style-type: none">• Anxiety/ depression• Diminished leisure, enjoyment• Loss of intactness or identity
Spiritual	<ul style="list-style-type: none">• Life's altered meaning• Question true relationship with "higher power"

Pain Assessment

Definition of Pain

“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage”
 – International Association for the Study of Pain, 1979

“Pain is whatever the experiencing person says it is, existing whenever he/she says it does”
 – Margo McCaffery

“The 5th Vital Sign”
 – American Pain Society



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Pain Types

Nociceptive	Inflammatory	Neuropathic
<ul style="list-style-type: none"> • Somatic • Visceral 		<ul style="list-style-type: none"> • Central • Peripheral

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Developmental Differences in Pain Expression

Infants	Toddlers	Young Children	School-Age
Body rigidity Inconsolable Poor oral intake Difficulty sleeping Irritable Quivering chin	Intense crying Aggression Regression Withdrawn Restless ↓ interest in play Difficulty sleeping	Verbalize pain Thrashing Push away pain Cling to parent Request support	Verbalize pain Objectively measure pain Stalling techniques Muscle rigidity Difficulty sleeping

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Principles of Pain Assessment

- Tailor assessment to child's age
 - Gold Standard is **SELF-REPORT**
- Earn child's trust for an honest report
- Use child's words for pain description
 - Hurt
 - Boo-boo
 - Owie
- Document pain regularly
- Do not rely only on...
 - Physiologic indicators
 - Behavioral indicators



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Hormonal/ Metabolic Changes

- Hyperglycemia
 - Decreased insulin secretion
 - Release of catecholamines
 - Epinephrine, norepinephrine
 - Increased release of glucagon, cortisol, and aldosterone
 - Increase rate of protein breakdown
 - Increased heart rate (HR), respiratory rate (RR), blood pressure (BP)
 - Palmar sweating
 - Decreased pO₂
 - Increased myocardial oxygen consumption
-

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Pain Assessment Scales

Infants <6 months	Toddlers 0-3 years	Young Children 3-6 years	School-Age >7 years
CRIES NIPS	FLACC CHEOPS	Poker chip scale Oucher scale Wong-Baker Faces	Visual analog scale Numeric rating

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Assume Pain Present (APP)

- Systematic process to evaluate pain in a non-verbal patient
- Observes
 - Behaviors
 - Patient history of painful condition
 - Illness, trauma, or surgery causes
 - Invasive and non-invasive painful procedures
 - Presence of instrumentation
 - Chest tubes
 - Ventilators

American Society for Pain Management Nursing

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Patient Case: Canter

12 year-old male awaiting cardiac transplant

What questions would you ask when assessing pain?

Patient Case: Canter

12 year-old male awaiting cardiac transplant

What type of pain is Canter experiencing?

- Pain all over his side and back
- “maybe” a headache
- No complaints of dyspnea or chest pain

What are the patient/parents’ expectations?

- Really want to keep him comfortable while they continue this long wait

Are the caregivers compliant with instructions?

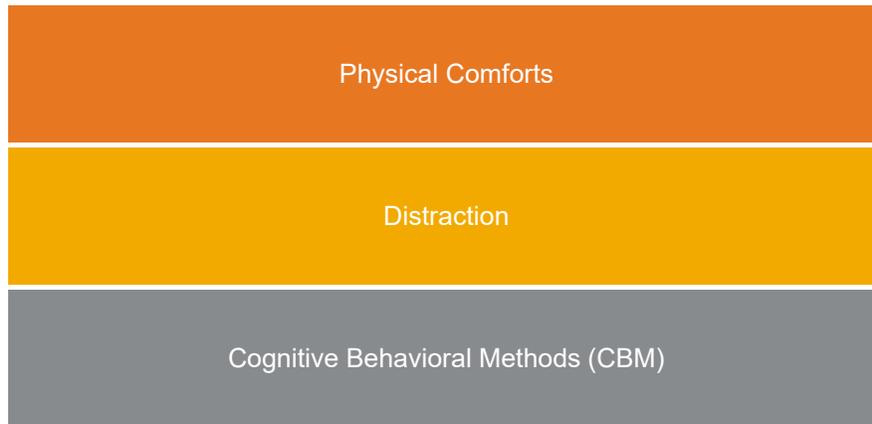
Other considerations?

- Risk for arrhythmias, bradycardia, electrolyte disturbances, respiratory depression
 - Drug interactions or QT interval prolongation?
-

Non-Pharmacological
Strategies

Non-Pharmacological Pain Management

Three categories of interventions



Non-Pharmacological Interventions

Infants (0-1 years)

Physical Comforts	Rocking, swaddling, kangaroo care, pacifier, sucrose, decrease light and noise, therapeutic touch, massage, aromatherapy
Distraction	Music, singing, soothing and familiar voice, bubbles, pacifiers, mobiles, lullabies
CBM	Parent support and guided teaching on how to increase patient's comfort

Non-Pharmacological Interventions

Toddlers & Pre-School Children (2-5 years)

Physical Comforts	Rocking, cuddling, pacifier, decreased light and noise, massage, TENS, therapeutic touch, heat/cold, acupressure, physical therapy, aromatherapy, Reiki
Distraction	Songs, music, pop-up books, videos, bubble-blowing, stories, clowning, pet visits
CBM	Art and music therapy, emotive imagery and hypnosis, play, relaxation games, story telling, simple explanations, parent support

Non-Pharmacological Interventions

School-Aged Children (6-11 years)

Physical Comforts	Rocking, cuddling, decrease light and noise, massage, TENS, therapeutic touch, positioning, heat/cold, acupressure, acupuncture, physical therapy, Reiki, yoga, meditation, reflexology
Distraction	Songs, music, pop-up books, puppets, toys and games, videos, bubble-blowing, stories, clowning, pet visits
CBM	Art and music therapy, imagery and hypnosis, play, relaxation games, participation in story-telling, psychotherapy, biofeedback, parent support

Non-Pharmacological Interventions

Adolescents (12-18 years)

Physical Comforts	Massage, TENS, therapeutic touch, positioning, heat/cold, acupressure, acupuncture, physical therapy, environment adjustment, Reiki, aromatherapy, yoga, meditation, reflexology
Distraction	Music, games, stories, pet visits
CBM	Imagery and hypnosis, art and music therapy, relaxation and deep breathing, information, biofeedback, psychotherapy, parent support

Patient Case: Canter

12 year-old male awaiting cardiac transplant

What possible non-pharmacological methods could we utilize for Canter's pain?

Patient Case: Canter

12 year-old male awaiting cardiac transplant

Non-Pharmacological Options

Physical Comforts	Massage, TENS, positioning , heat/cold, acupressure, acupuncture, physical therapy , meditation
Distraction	Music, games, videos
CBM	Imagery and hypnosis, play, relaxation games

Pain Management Principles

Principles of Pain Management:

Four concepts to remember

<i>by the</i> ROUTE	Use the least invasive, most convenient route
<i>by the</i> CLOCK	Administer scheduled medications Provide rescue doses as needed (10-20% of daily dose)
<i>by the</i> CHILD	Tailor therapy to child's circumstance, needs, and response
<i>by the</i> LADDER	Escalate by 2-step analgesic ladder

Principles of Pain Management: *by the route*

Oral Feeding Tube	<ul style="list-style-type: none"> • Painless • Consider taste • Easy to titrate; Liquid & tablet formulations • Not recommended in bowel obstruction or severe nausea/vomiting
Rectal	<ul style="list-style-type: none"> • Consider patient preference and privacy • Wide variability in therapeutic blood levels • Use caution in neutropenic or thrombocytopenic patients • Useful in patients unable to swallow or with significant vomiting
Intranasal	<ul style="list-style-type: none"> • May cause nasal irritation if solution is not isotonic • Requires small volume (0.1 mL per nare) • Divide the dose between nares • Atomizer device provides better absorption than drops
Transdermal	<ul style="list-style-type: none"> • Painless • Requires opioid tolerance prior to initiating • Difficult to titrate; Patch cannot be cut or folded • May have increased absorption in febrile patients or young children

Principles of Pain Management: *by the route*

Intravenous	<ul style="list-style-type: none"> • Rapid pain control • Easiest to titrate and adjust quickly • Severe vomiting, mucositis, bowel obstruction, or poor absorption • Invasive; Requires equipment and electricity
Patient Controlled Analgesia (PCA)	<ul style="list-style-type: none"> • Eliminates time between pain perception and relief • Basal maintenance rate, as well as breakthrough doses • Requires understanding of button push and pain relief • Maximum amounts can be set to minimize the risk of overdose
Subcutaneous	<ul style="list-style-type: none"> • Small, portable pump • Can be used for continuous infusion or PCA • Bioavailability affected by fat, muscle, and water composition • Minimize volume to decrease discomfort (Max volume: 2 mL)
Intramuscular	<ul style="list-style-type: none"> • Painful • Fluctuations in absorption (decreased muscle mass) • Adequate blood flow to the injection site to ensure absorption • Minimize volume (neonates- 0.5 mL, infants- 1 mL, children- 2 mL)

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Principles of Pain Management

by the clock

- Schedule analgesia around the clock
 - Convert to long-acting opioid or extended-release formulation
 - Once pain management goal achieved and opioid requirements stable
- Provide short-acting opioid for rescue therapy
 - 5-15% of 24 hour total around-the-clock dose



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Principles of Pain Management

by the child

- Tailor therapy to child's circumstance, needs, and response
- Complete medical history
 - History of gastritis, ulcers, gastrointestinal bleeding, or thrombocytopenia
 - Presence of liver or renal dysfunction: *May need dosage adjustment*
 - Disease progression
 - Associated symptoms: *nausea, anorexia, sleep disturbances*
 - Sources of pain: *neuropathic, bone, visceral, intracranial pressure, muscle*
 - Medication allergies
 - Current medications for potential drug interactions
 - History of medication misuse or substance abuse in patient or family
 - Previous opioid exposure and response: *Start low, go slow if opioid-naïve*

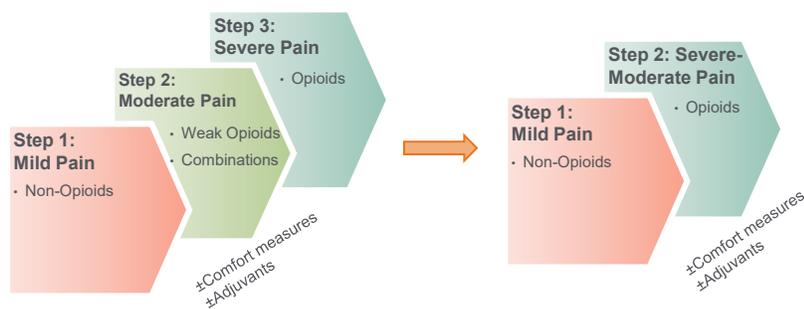
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Principles of Pain Management

by the ladder

- Adult Model

- Child Model



World Health Organization, ed. Cancer pain relief and palliative care in children. Geneva: World Health Organization, 1998.

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Principles of Pain Management

by the ladder

- Medication classifications
 - Non-opioid analgesics
 - Opioid analgesics
 - Adjuvant analgesics
 - Use in conjunction
 - Maximize analgesia
 - Minimize toxicity
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Non-Opioid Analgesics

Peripheral Analgesics

- Peripheral inhibition of prostaglandin synthesis
 - Ceiling effect
 - Watch maximum doses
 - Synergistic with opioids
 - acetaminophen (Tylenol®)
 - Non-steroidal anti-inflammatory drugs (NSAIDs)
 - ibuprofen (Motrin®, Advil®)
 - naproxen (Aleve®)
-

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acetaminophen (Tylenol)

- Pharmacokinetics
 - Metabolized via sulfation and glucuronidation
 - Age restrictions
 - None
 - Side effects
 - Potential for hepatotoxicity at higher doses
 - Routes available
 - PO (tablets & liquid), PR, IV
 - Equal efficacy with IV and PO
 - Typical starting dose
 - PO: 10-15 mg/kg q4-6h prn
 - Max: 90 mg/kg/day (3,000 mg/day)
-

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ibuprofen

- Pharmacokinetics
 - Metabolized via glucuronidation, oxidation, and CYP enzymes
 - Age restrictions
 - FDA approved >6 months of age
 - Side effects
 - Gastrointestinal and renal toxicities
 - Caution in pediatric oncology patients with thrombocytopenia
 - Routes available
 - PO (tablets & liquid), IV
 - Typical starting dose
 - PO: 5-10 mg/kg q6-8h prn
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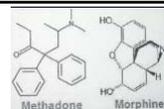
Opioid Principles

Central Analgesics

- Mediate analgesia by binding to specific opioid receptors in CNS
 - No ceiling effect
 - Adverse reactions
 - Metabolized by the liver
 - Tolerance
 - Dependence
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Opioid Classes



Phenanthrenes

morphine
codeine
oxyCODONE
HYDROmorphine
oxyMORphone
HYDROcodone
nalbuphine
butorphanol

Phenylpiperidines

fentaNYL
meperidine

Diphenylheptanes

methadone

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Common Opioid Side Effects

- Constipation
 - Stool softener/ stimulant
 - Start prophylactically
 - Nausea/ Vomiting
 - Antiemetic
 - ↓ dose
 - Sedation
 - Stimulant
 - ↓ dose
 - Pruritis/ urticaria
 - Rotate opioid to a more synthetic form
 - Antihistamine
 - Naloxone low dose drip
 - Hallucinations/ nightmares
 - ↓ dose
 - Rotate opioid
 - Dysphoria/ delirium
 - Rotate opioid
 - Myoclonus/ seizures
 - Rotate opioid
 - Respiratory depression
 - ↓ dose
 - Rotate opioid
 - Naloxone
-

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General Opioid Black Box Warnings

- US Black Box Warnings
 - Extended or sustained release dosage forms should not be crushed or chewed
 - Indicated for the management of moderate to severe pain
 - Do not administer with alcohol
 - Healthcare providers should be alert to problems of abuse, misuse, or diversion
 - Serious, life-threatening, or fatal respiratory depression may occur
 - Accidental consumption in children can result in fatal overdose
 - Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome
 - Special Warnings
 - Potentially harmful interactions with other medications leading to serotonin syndrome
 - Combination with benzodiazepines or other medications that depress the CNS may result in serious adverse reactions, including respiratory depression or death
 - Inadequate cortisol production
-

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Pain Management Considerations

- Duration of action of medication may not correlate with half-life
 - Utilize equianalgesic dose when converting
 - Less drug is typically required to prevent pain than treat pain
 - Assess efficacy at regular intervals
 - Taper off opioids
-

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Opioid Pharmacokinetics

Drug	Peak (hr)	Half-life (hr)	Onset (min)	Duration (hr)
morphine	0.5-1	2	10-20	3-5
HYDROmorphine	0.5-1	2-3	10-20	3-5
HYDROcodone	1	4	30-60	4-6
codeine	0.5-1	3	10-20	4-6
oxyCODONE	0.5-1	2-3	30-60	4-6
meperidine	0.5-1	2-4	10-20	2-5
fentaNYL	10-20	2-4	7-15	1-2
methadone	0.5-1	15-30	10-20	>8 (chronic)

Adapted from Reisine T, Paternak G 1995 and Pasero C, Portenoy RK, McCaffery M. 1999

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Equianalgesic Chart

Opioid	Intravenous or Subcutaneous	Oral
Morphine (MSContin®, Roxanol®)	10 mg	30 mg
Oxycodone (Oxycontin®, Percocet®*)	--	20 mg
Hydromorphone (Dilaudid®)	1.5 mg	7.5 mg
Hydrocodone (Lortab®*, Vicodin®*)	--	30 mg
Oxymorphone (Opana®)	1 mg	10 mg
Fentanyl Transdermal (Duragesic®)	<u>1 mcg/hr fentanyl = 2 mg/24 hrs PO morphine</u> 100 mcg/h approx. Morphine 200 mg/24hrs 25 mcg/h approx. Morphine 50 mg/24 hrs	

*In combination with acetaminophen

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Equianalgesic Dosing

$$\frac{\text{Equianalgesic Variable}}{\text{Total 24 hour Opioid}} = \frac{\text{Equianalgesic Variable (x)}}{\text{Total 24 hour Opioid (x)}}$$

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Equianalgesic Dosing

$$\frac{\text{Equianalgesic Variable}}{\text{Total 24 hour Opioid}} = \frac{\text{Equianalgesic Variable (x)}}{\text{Total 24 hour Opioid (x)}}$$

↑ Divide
← Multiply

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Example Equianalgesic Conversion

Calculate Morphine Equivalent Daily Dose (MEDD)

- morphine 5 mg x 3 doses= 15 mg
 - HYDROcodone 5 mg x 6 doses= 30 mg
- 1:1 equianalgesic with morphine

$$\frac{30 \text{ mg HYDROcodone}}{30 \text{ mg HYDROcodone}} = \frac{30 \text{ mg morphine}}{\text{MEDD}}$$

- 15 mg (morphine) + 30 mg (HYDROcodone) = 45 mg MEDD
-

Example Equianalgesic Conversion

Conversion to oxyCODONE

Calculated MEDD = 45 mg

$$\frac{30 \text{ mg morphine}}{45 \text{ mg MEDD}} = \frac{20 \text{ mg oxyCODONE}}{x \text{ mg oxyCODONE}}$$

Total equivalent daily dose oxyCODONE = 30 mg

Equianalgesic Dosing

- Cross tolerance
 - Decrease calculated dose by 30%

 - Factors affecting dose selection
 - Dosage forms available
 - Current level of pain control
 - Adverse effects
 - Other medication changes
 - Non-pharmacological interventions
-

Example Equianalgesic Conversion

Conversion to oxyCODONE

Calculated oxyCODONE = 30 mg per day

- Decrease by 30% for incomplete cross tolerance
oxyCODONE 18 mg/day

Dose range 18 – 30 mg/day

Dosage forms available

- Extended release tablets: 10, 15, 20, 30, 40, 60 mg
- Immediate-release tablets: 5, 15, 30 mg
- Solution: 5 mg/5 mL

Potential dose options*

- oxyCODONE ER 10 mg q12h
- oxyCODONE ER 15 mg q12h
- oxyCODONE IR 5 mg q6h
- oxyCODONE IR 7.5 mg q6h

*ER formulations would be inappropriate for GT administration

Breakthrough Dosing

- Immediate-release products
- 10-20% of total 24 hour dose

Example Breakthrough Dosing

Conversion to oxyCODONE

Calculated dose range: 18-30 mg oxyCODONE per day

- 10-20% for breakthrough dosing

Dosage forms available

- Immediate-release tablets: 5, 15, 30 mg
- Solution: 5 mg/5 mL

Potential dose options

- oxyCODONE IR 2-6 mg q4h prn
-

Opioid Titration

- Use of ≥ 3 breakthrough doses per day
 - Increase long-acting medication 25-30%
 - General opioid dose increases
 - Mild-moderate pain: 25-50%
 - Moderate-severe pain: 50-100%
 - Frequency of titration
 - Short-acting medications: q2h
 - Long-acting medications: q24h
 - Fentanyl transdermal patch: q72h
 - Methadone: q5-7 days
-

Opioids

codeine

- Pharmacokinetics
 - Metabolized via CYP2D6 to morphine
 - Poor metabolizers deficient in CYP2D6 = inadequate therapeutic response
 - 35% of children may have inadequate conversion
 - Ultra-rapid metabolizers = supratherapeutic response
- Age restrictions
 - Not recommended in children
- US boxed warning
 - Respiratory depression and death following tonsillectomy/adenoidectomy
- Routes available
 - PO (tablets)
 - PO in combination with acetaminophen (liquid & tablets)
- Typical starting dose
 - >6 months: 0.5-1 mg/kg q4h prn

traMADol

- Weak opioid w/ serotonin & norepinephrine modulation & alpha-2 agonism
 - Potential effectiveness for neuropathic pain
 - Pharmacokinetics
 - Metabolized via CYP2D6 to O-desmethyltramadol
 - Age restrictions
 - FDA approved >18 years of age
 - US boxed warning
 - Respiratory depression and death following tonsillectomy/adenoidectomy
 - Side effects
 - Lowers the seizure threshold
 - Routes available
 - PO, topical
 - Typical starting doses
 - PO: 1-2 mg/kg q4-6h prn
 - Max: 8 mg/kg/day
-

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oxyCODONE

- Pharmacokinetics
 - Clearance is higher (up to 50%) in children aged 2-20 years
 - Results in shorter half-life
 - Age restrictions
 - FDA approved >18 years of age
 - Routes available
 - PO, SL, PR
 - PO in combination with acetaminophen
 - Typical starting dose
 - PO: 0.1-0.2 mg/kg q4h prn
-

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morphine

- Pharmacokinetics
 - Delayed clearance in infants <6 months of age
 - Glucuronidation → morphine-3-glucuronide metabolite
 - Accumulation can contribute to neurotoxicity
- Age restrictions
 - None
 - Infants have increased risk of respiratory depression
- Routes available
 - PO, SL, PR, IV, SC, IM, epidural, intrathecal
- Typical immediate-release starting doses
 - <6 months:
 - PO/SL: 0.08 mg/kg q6h prn
 - IV/IM/SQ: 0.02 - 0.03 mg/kg q6h prn or 0.01 mg/kg/hr
 - >6 months:
 - PO/SL: 0.2 - 0.5 mg/kg q4h prn
 - IV/IM/SQ: 0.05 mg/kg q2h prn or 0.01 mg/kg/hr

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HYDROcodone

- Pharmacokinetics
 - Metabolized via CYP2D6 to hydromorphone
- Age restrictions
 - Immediate-release products with acetaminophen
 - FDA approved >2 years of age
 - Extended-release products
 - Adult only dosing
- Routes available
 - PO (tablets, extended-release)
 - PO in combination with acetaminophen (tablets, capsules, & liquid)
- Typical starting dose
 - >2 years: 0.1 – 0.2 mg/kg q4h prn

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HYDROmorphine

- Pharmacokinetics
 - Glucuronidation → hydromorphone-3-glucuronide metabolite
 - Accumulation can contribute to neurotoxicity
- Age restrictions
 - Not recommended <6 months of age
- Routes available
 - PO, SL, PR, IV, SC, epidural, intrathecal
- Typical starting doses
 - PO: 0.03-0.08 mg/kg q4h prn
 - IV: 0.015 mg/kg q3h prn or 0.003 - 0.005 mg/kg/hr

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fentaNYL

- Pharmacokinetics
 - Plasma concentrations twice as high in children <5 years of age via transdermal
 - Half-life is longer in preterm infants
 - Becomes similar to adults within first months of life
- Age restrictions
 - IV & transdermal FDA approved >2 years of age
 - Transmucosal FDA approved >18 years of age
- Routes available
 - Transmucosal, transdermal, IV
 - Substantial differences in pharmacokinetic profile of different fentaNYL products
- Typical starting dose
 - Patch: 30-60 mg/day morphine = 12.5 mcg/hr patch
 - IV : 1 - 2 mcg/kg q1h prn or 0.5 - 2 mcg/kg/hr

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methadone

- Pharmacokinetics
 - Substrate and inhibitor of CYP450 enzymes
 - Long and unpredictable half-life
 - Little data on pharmacokinetics in young children and infants
 - Duration of analgesia shorter than half-life
 - Age restrictions
 - None
 - US boxed warning
 - Life-threatening respiratory depression
 - QT interval prolongation and serious arrhythmia
 - Routes available
 - PO, SL, PR, IV, SC
 - Long-acting even via liquid or crushed tablet
 - Typical starting dose
 - PO: 0.1-0.2 mg/kg q8-12h
-

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Benefits of methadone

- Long-acting synthetic opioid
 - Affinity for mu & delta receptors
 - N-methyl-D-aspartate (NMDA) receptor antagonism
 - Norepinephrine and serotonin reuptake inhibition
 - Decreased incidence of tolerance
 - Beneficial for neurotoxicity
 - Structurally different than other opioids
 - No toxic metabolites
 - Safe in renal and hepatic impairment
 - Appropriate for patients with swallowing limitations
 - Multiple cost-effective, long-acting, oral dosage forms
 - Multiple routes of administration
-

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Patient Case: Canter

12 year-old male awaiting cardiac transplant

Is Canter a candidate for methadone?

Patient Case: Canter

12 year-old male awaiting cardiac transplant

Is Canter a candidate for methadone?

- Drug interactions?
 - Cardiac risk factors?
 - Renal function?
 - Concerns for drug diversion in home?
-

Example Conversion to Methadone

Calculate Morphine Equivalent Daily Dose (MEDD)

- Morphine 5 mg x 3 doses= 15 mg
- Hydrocodone 5 mg x 6 doses= 30 mg (1:1 with morphine)
- 15 mg + 30 mg= 45 mg MEDD

Convert to methadone

- 45 mg x 0.2 = 9 mg
- Decrease dose due to incomplete cross tolerance
9 mg x 0.6= 5.4 mg
- Divide by 2 for q12h dosing

Methadone 2.5 mg q12h

Age Restrictions of Analgesics

Medication	FDA Approved Age	Concerns
aspirin	>12 years	Reye's syndrome
codeine	Adults	Black Box Warning <ul style="list-style-type: none"> • Respiratory depression • Variable pharmacokinetics
hydrocodone	>2 years <ul style="list-style-type: none"> • Oral solutions • With acetaminophen 	CYP2D6 metabolism
oxyCODONE	>18 years	CYP2D6 metabolism
traMADol	>16 years	CYP2D6 metabolism Decreases seizure threshold
ibuprofen	>6 months	Hepatic metabolism <ul style="list-style-type: none"> • CYP2D6 (and others) • Glucuronidation
HYDROmorphine	>6 months	Glucuronidation
fentaNYL	>2 years <ul style="list-style-type: none"> • Off-label IV use common 	Dosage forms <ul style="list-style-type: none"> • Transdermal patch • Transmucosal

Opioid Selection Based on Organ Function

	Preferred	Consider	Avoid
Hepatic Failure	HYDROmorphine morphine methadone	oxyCODONE fentaNYL	codeine HYDROcodone meperidine traMADol
Renal Failure	fentaNYL methadone oxyCODONE	HYDROmorphine HYDROcodone	morphine codeine traMADol meperidine
Hepato-Renal Syndrome	HYDROmorphine methadone	fentaNYL oxyCODONE	morphine codeine traMADol HYDROcodone meperidine

Hunt MO, Probus BM, Winters JP, Parker DC. Pediatric Palliative Care Consultant: Guidelines for Effective Management of Symptoms. Dublin, Ohio: Hospiscript, a Catamaran Company; c2014.

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Adjuvant Agents

Adjuvant Medications

- Drug whose primary indication is not to treat pain, but have analgesic properties in specific painful conditions
 - Common conditions
 - Neuropathic pain
 - Bone pain
 - Common drug classes
 - Antidepressants
 - Anticonvulsants
 - Corticosteroids
-

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gabapentin

- Anticonvulsant medication commonly used for neuropathic pain
 - Pharmacokinetics
 - Clearance is highly variable in infants
 - Age restrictions
 - FDA approved >3 years of age
 - Side effects
 - Sedation: titrate as tolerated to effective dose
 - Nystagmus, thought disorder, hallucinations, headache, weight gain, myalgia
 - Routes available
 - PO
 - Typical starting dose
 - PO: 2-5 mg/kg QHS - TID, titrated over 2-4 weeks
 - Max: 10-20 mg/kg TID
-

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pregabalin

- Anticonvulsant medication commonly used for neuropathic pain
 - Age restrictions
 - FDA approved in adults
 - Side effects
 - Edema, thrombocytopenia, prolong QT interval, rhabdomyolysis
 - Dizziness, somnolence, visual disturbances, xerostomia, weight gain
 - Suicidal ideation
 - Routes available
 - PO
 - Solution, capsules
 - Typical starting dose
 - Adult: 150 mg/day divided; Max 100 mg TID
-

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Tricyclic Antidepressants (TCAs)

- Commonly used for neuropathic pain
 - Analgesia may be seen 3-7 days after initiation
 - Age restrictions
 - amitriptyline: FDA approved >12 years of age
 - desipramine: FDA approved in adolescents
 - nortriptyline: FDA approved in adolescents
 - US Boxed Warning
 - Suicidal ideation in adolescents and young adults
 - Side effects
 - Sedation, dry mouth, blurred vision, constipation, urinary retention
 - EKG recommended prior to initiation
 - QT prolongation, Wolf-Parkinson-White Syndrome
 - Desipramine and nortriptyline may have fewer side effects than amitriptyline
 - Routes available
 - PO
 - Typical starting dose
 - PO: 0.1 mg/kg qhs
 - Titrate dose weekly based on tolerance and response
-

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DULoxetine

- Serotonin & norepinephrine reuptake inhibitor (SNRI)
 - Age restrictions
 - FDA approved in adults
 - Including diabetic peripheral neuropathic pain
 - US Boxed Warning
 - Suicidal ideation in adolescents and young adults
 - Contraindications
 - Hepatic failure
 - Narrow-angle glaucoma
 - Side effects
 - Somnolence, fatigue
 - Routes available
 - PO
 - Typical starting dose
 - 30 mg qday
-

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Corticosteroids

- Used for the treatment of bone and visceral pain
 - May increase energy and appetite
 - Pharmacokinetics
 - Dexamethasone provides potent anti-inflammatory effects with minimal mineralocorticoid
 - Age Restrictions
 - None
 - Side effects
 - Depression, insomnia, mood swings, personality changes
 - Adrenal suppression, immunosuppression
 - Osteoporosis and inhibition of bone growth
 - Routes available
 - PO, IV, IM
 - Typical starting doses
 - Dose based on condition and child's response to therapy
 - predniSONE: 0.05 - 2 mg/kg/day divided 1-4 times per day
 - dexamethasone: 0.02 – 0.3 mg/kg/day divided q6-12h
-

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Patient Case

Patient Case: Canter

12 year-old male awaiting cardiac transplant

Listed IB for transplant (failed Fontan) on ambulatory milrinone

Recently discharged from the hospital after prolonged course now being followed by palliative care

Weight: 24 kg Height: 127 cm

Lives at home; Mom is primary caregiver

PMH:

- Complete AV canal and total anomalous pulmonary venous return connection status post Fontan
 - Failing physiology with ventricular dysfunction
 - History of thromboembolism

CC:

- Increasing side/back/abdominal pain and headaches
- Slow decline of appetite and energy since initial transplant evaluation/listing

Allergy: NKDA

Patient Case: Canter

12 year-old male awaiting cardiac transplant

Medications	Directions
acetaminophen (Tylenol®)	325 mg po q6hrs <i>13.5 mg/kg/dose</i>
amoxicillin	250 mg po BID
famotidine (Pepcid®)	20 mg po daily
furosemide (Lasix®)	40 mg po BID <i>1.7 mg/kg/dose</i>
milrinone	0.5 mcg/kg/min IV continuous infusion <i>via PICC line</i>
spironolactone/ hydrochlorothiazide (Aldactazine®)	25 mg po daily <i>~1 mg/kg/dose</i>
warfarin (Coumadin®)	3 mg po daily

Patient Case: Canter

12 year-old male awaiting cardiac transplant

What recommendations would you make for managing Canter's pain?

Patient Case: Canter

12 year-old male awaiting cardiac transplant

Recommendations

- Non-pharmacological interventions
 - Non-opiate analgesics
 - Any contraindications?
 - Scheduled vs PRN?
 - Opiates
 - Morphine 2.5 mg (0.1 mg/kg/dose) po q4hrs prn pain
 - Use a log to document/track
 - Monitoring?
 - PO vs IV?
 - Can we use enteral route?
 - Compatibility
 - Adjuvant agents (what kind of pain?)
 - When to escalate/call?
-

Summary

- Children experience pain similar to adults
 - Similar approach to pain management as adults
 - Age-appropriate assessment strategies
 - Age-appropriate non-pharmacological treatment
 - Patient specific medication selection
 - Tailor therapy to child's circumstance, needs, and response
 - Dose medications by weight
 - Consider route, scheduled medications, and 2-step analgesic ladder
-

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Questions?

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Normal Pediatric Values

Normal Pediatric Respiratory Rates (RR)

Age (years)	Mean RR (breaths/min)
0-2	25-30
3-9	20-25
10-18	16-20

Normal Pediatric Heart Rates (HR)

Age	Mean Heart Rate (beats/min)	Heart Rate Range (beats/min)
<1 day	123	93-154
1-2 days	123	91-159
3-6 days	129	91-166
1-3 weeks	148	107-182
1-2 months	149	121-179
3-5 months	141	106-186
6-11 months	134	109-169
1-2 years	119	89-151
3-4 years	108	73-137
5-7 years	100	65-133
8-11 years	91	62-130
12-15 years	85	60-119

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Pediatric Assessment Scales

CRIES

- Intended for infants (0-6 months old)
- Five item scale, each item scored 0-2
 - Crying
 - Typical cry of pain is high pitched
 - Required O₂ for SaO₂ < 95%
 - Babies in pain experience deoxygenation
 - Increased vital signs
 - BP and HR
 - Expression
 - Pain expression typically is a grimace
 - Sleepless
 - Record child's state during previous hour

<http://prc.coh.org/pdf/CRIES.pdf>

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Neonatal Infant Pain Scale

NIPS

- Intended for preterm and full-term neonates
- Six item scale, item score varies from 0-1 or 0-2
 - Facial expression
 - Relaxed or grimace
 - Cry
 - No cry, whimper, or vigorous crying
 - Breathing patterns
 - Relaxed or change in breathing
 - Arms & Legs
 - Restrained, relaxed, flexed, or extended
 - State of arousal
 - Sleeping, awake or fussy

Lawrence J Alcock D et al. The development of a tool to assess neonatal pain. Neonatal Network. 1993; 12 (6 September): 59-66.

FLACC Behavioral Scale

Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or "talking to". Distractible	Difficult to console or comfort

Merkel S, Voepel-Lewis T, Shayevitz J, et al. *The FLACC: A behavioral scale for scoring postoperative pain in young children.* Pediatric Nursing. 1997, 23: 293-297.

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Wong-Baker Faces

- Intended for children ages 3 and older

Wong-Baker FACES™ Pain Rating Scale



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Oucher Scale

- Intended for children ages 3 and older



<http://www.oucher.org/>

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Visual Analog Scale (VAS) & Numeric Rating Scale

- Visual analog scale
 - Intended for children ages 7 and older
 - Ask child to point to the area along the line that represents their pain



- Numeric rating scale
 - Intended for children ages 9 and older
 - Ask child to rate his/her pain on a scale of 0-10

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CHEOPS

Children's Hospital of Eastern Ontario Pain Scale

- Intended for post-op pain in children ages 0-4
- Six item scale, scores range from 4-13
 - Cry
 - No cry to screaming
 - Facial
 - Smiling to grimace
 - Child verbal
 - Positive to both pain and non-pain complaints
 - Torso
 - Neutral to restrained
 - Touch
 - Not touching to restrained
 - Legs
 - Neutral to restrained

Poker Chip Scale



- Intended for children ages 3-6
- Quantifies pain intensity by using four poker chips to represent amounts of pain
 - 1 chip – “a little bit of hurt”
 - 2 chips – “a little more hurt”
 - 3 chips – “more hurt”
 - 4 chips – “the worst hurt ever”
- Ask child to say how many “pieces of hurt” they are having
- Then ask child to tell more about their hurt