Pediatric Palliative Care Approach to Pain & Symptom Management

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Revised by the BCH/DFCI Pediatric Palliative Care Approach to Pain & Symptom Management Committee in November 2023.

Dana-Farber Cancer Institute/Boston Children's Hospital Pediatric Palliative Care Approach to Pain & Symptom Management (Blue Book) is a pocket-guide to symptom management in children, a tool for identifying areas for self-study, and provides educational information for healthcare professionals at Dana-Farber and Boston Children's Hospital. This information is not medical advice. Seek the Boston Children's Hospital formulary / Lexicomp for current medication dosing, formulations, interactions, and side effects. The Blue Book is not continually updated, and new safety information may emerge after the most recent publication date. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Use of medications requires adequate knowledge of side effects and drug-drug interactions. Many of these medications involve off-label use. Official prescribing information should be consulted before any product is used or recommendation made. Non-pharmacologic interventions are always an essential part of symptom management.

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Important Definitions

Addiction/Substance Use Disorder: A primary, chronic, neurobiological disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Agitation: Unpleasant state of arousal manifesting as irritability, restlessness, and increased motor activity.

Chronic Pain: Pain that recurs for more than 3 months; requires a distinctly different approach from acute pain that can benefit from specialty involvement.

Diversion: The redirection of a prescription drug from its lawful purpose to illicit use.

GMFCS (Gross Motor Function Classification System): 5 level clinical classification system that describes the gross motor function of individuals with cerebral palsy (CP). Children with level 4 or 5 have are at increased risk for neuro-pain.

Harmful Drug Use: Self-administration of medications to alter one's state of consciousness. This is a maladaptive pattern of use of a medication leading to significant impairment or distress, and potentially leading to opioid or substance use disorders. Previously referred to as abuse, which has fallen out of favor since it uses stigmatizing, non-person-first language.

Irritability: An abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an acute illness, or a medical condition.

Misuse: Use of a medication with therapeutic intent, but other than as directed, regardless of whether a harmful outcome occurs. Examples of misuse include taking an extra dose or opioid for uncontrolled pain, outside of how it was prescribed or altering of the route of delivery.

Neuro-Pain: Chronic pain sources due to alterations in the nervous system without diagnostic tests or features to differentiate one from another (i.e. central neuropathic pain, autonomic dysfunction, visceral hyperalgesia, chronic post-surgical pain), often with other co-morbid problems with overlapping features (spasticity, dystonia, seizures). Neuro-pain is recommended over neuro-irritability; word choice can impact how the problem is viewed.

Neuropathic Pain: Pain that arises from an alteration, insult and/or disease in the somatosensory nervous system.

Nociceptive Pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors; further broken down into visceral and somatic types.

Opioid Use Disorder: Diagnosis defined in the DSM-5, characterized by the compulsive use of opioids despite adverse events from continued use and signs of withdrawal when stopped.

Pain Behaviors: Observable features expressed without words by an individual in pain.

***Physical Dependence:** A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Pseudo-Addiction: Condition resembling drug addition, caused by undertreatment of symptoms causing the patient to seek more medication.

***Tolerance:** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Withdrawal: The symptoms that occur when medications are stopped abruptly in a patient who has been chronically (most often opioids/ benzodiazepines) and has their dose stopped or reduced by greater than 50% abruptly. These symptoms include but are not limited to anxiety, agitation, muscle aches, sweating, diarrhea, nausea and vomiting.

***Opioid Tolerance** and **Physical Dependence:** Expected with long-term opioid treatment and should not be confused with addiction, which manifests as drug abuse behavior. The presence of opioid tolerance and physical dependence does not equate with addiction.

PACT Language	
Instead of	**Say/Write**
Complain	Endorse
Narcotic	Opioid
Compliance	Adherence
Refuse	Decline
Need	Consider

Evaluation & Approach to Pain Management[1, 2]	
1. Comprehensive assessment and workup as needed to make accurate diagnosis. Pain has a differential diagnosis. 2. Consider non-pharmacologic interventions and specific treatments 3. Use non-opioid agents (acetaminophen, ibuprofen) a. Scheduled non-opioids are preferred to PRN in continuous / uncontrolled pain 4. Add opioids and titrate dose as needed a. Schedule opioids or convert to long-acting opioid if ≥ 3 as-needed doses used per day 5. Assess response closely and adjust opioid dose as needed a. Right dose is patient specific and determined by benefit and side effects; there is no "max" dose	↕ - *Integrative therapies* and *adjuvants* should be continually considered to achieve broad spectrum analgesia - Consider adjuvants before opioids for neuropathic pain and children with impairment of the CNS *(See page 17-20)* ↕

Non-Opioids for Mild Pain		
Medication	**Initial Dose**	**Comments**
Acetaminophen 160 mg/5mL Supp: 120mg, 325mg, 650mg tabs	< 32kg: PO or IV – 12.5mg/kg/dose q4hr scheduled or PRN pain/fever (max = 75mg/kg/day) >/= 32kg: PO or IV – 500mg/dose q4hr scheduled or PRN pain/fever (max = 000mg/day)	< 2 g/day appears to be well tolerated in adult patients with cirrhosis, monitor closely; no anti-inflammatory activity; low risk of GI side effects; no effect on platelets IV formulation avoids first pass hepatic metabolism and may reduce chance of hepatic injury. IV & PO considered to provide equal analgesia
Ibuprofen 40mg/mL, 100mg/5 mL; 100mg, 200mg, 400mg, 600mg tabs	PO: 6-10 mg/kg (400-600mg) q6-8hr	Avoid in severe hepatic impairment and thrombocytopenia; may cause nephrotoxicity; avoid in infants <6 months (*see page 31 for rationale*)
Naproxen 125mg/5 mL; 250mg tabs	PO: 5-7 mg/kg (250-400mg) q12hr	↑ hepatotoxicity incidence versus other NSAIDs (↓dose 50% in hepatic disease); avoid in thrombocytopenia; may cause nephrotoxicity
Ketorolac 10mg tabs	IV: 0.3-0.5 mg/kg (15-30mg) q6-8hr Max 24-hour dose: 120mg IV PO: 10mg q6-8hr *adult dosing Max 24-hour dose: 40mg PO	Avoid use longer than 5 days; avoid in thrombocytopenia; may contribute to nephrotoxicity
Celecoxib 25 mg/mL; 50mg, 100mg caps	PO: 1-2 mg/kg (100-200mg) q12-24hr	↓ incidence of GI ulcerations; minimal to no inhibition of platelet function; avoid in sulfonamide allergy; black box warning of serious cardiovascular thrombotic events *in adults*

Opioids for Severe Pain						
Medication Formulations	**Initial Dose PO***	**Initial PO Dose >50kg**	**Initial Dose IV***	**Long Acting Formulations**	**Hepatic Metabolism[3]**	**Renal Excretion[4]**
TraMADol 50mg tab	1-2mg/kg PO q4-6hr	50-100mg q4-6hr PO	N/A	ER 100mg, 200mg, 300mg tabs Max 400mg/day	Prolong dose interval to q12h and avoid ER formulations in liver impairment	Prolong dose interval to q12h in renal impairment; may ↑ seizure threshold ± uremia
OxyCODONE 5mg/5mL Concentrate: 100mg/5mL 5mg, 10mg, 15mg, 20mg, 30mg tabs	0.1-0.2 mg/kg (5-10 mg) q4-6hr PO	5-10mg q4-6hr PO	N/A	OxyCONTIN 10mg, 20mg, 30mg, 40mg, 60mg tabs	Half-life ↑, clearance ↓, Peak plasma conc. ↑ Dose reduce by 30-50% and prolong intervals in liver impairment	Half-life ↑ Reduce dose by at least 50%; avoid in mod-severe impairment; avoid in dialysis
Morphine 10mg/5mL 20mg/1mL 15mg, 30mg tabs	0.2-0.3 mg/kg q3-4hr PO	15-20mg q3-4hr PO	0.05-0.1 mg/kg (2.5-5 mg) q2-4hr IV	MS Contin 15mg, 30mg, 60mg, 100mg, 200mg tabs	↑ bioavailability ↑ half-life, ↓ clearance w/ cirrhosis	Reduce dose by 25-50%, up to 75% with moderate impairment. Use 10:20 IV:PO ratio rather than 10:30 with renal impairment; avoid in ESRD due to accumulation of active metabolites
HYDRO-morphone 1mg/mL 2mg, 4mg, 8mg tabs	0.04-0.08 mg/kg (1-2 mg) q3-4hr PO	2-4mg q3-4hr PO	0.015 mg/kg (0.2-0.6 mg) q2-4hr IV	Not available in USA	Preferred drug in liver impairment; may need dose reduction 25-50% with severe disease	Dose reduce 50-75% with renal impairment; drug accumulates though considered safe in mild ESRD; dialyzable
FentaNYL	*(See page 8) for TD FentaNYL*		0.5-2 mCg/kg (25-75 mCg) q30minIV	*(See page 8)*	↑half-life Dose reduce TD patch by 50% with liver impairment;	Reduce dose by 25-50%, Preferred drug in renal impairment; not dialyzable
Methadone	*(See page 9-10)*			*(See page 9)*	Generally considered safe, may accumulate with repeated doses	Not dialyzable, preferred drug in renal disease
*Infants < 6 months require lower dosing, *see page 31**						

Patient Controlled Analgesia (PCAs)[5] starting dose recommendations for opioid naïve pediatric patient*			
Medication	**Morphine**	**HYDROmorphone**	**FentaNYL**
Loading Dose	Loading: 0.03 mg/kg	Loading: 0.006 mg/kg	0.3 mCg/kg
Continuous Infusion	0.015 mg/kg/hr	0.003 mg/kg/hr	0.15 mCg/kg/hr
"Demand" Dose	0.025 mg/kg	0.005 mg/kg	0.25 mCg/kg
Lockout Interval	7-12 minutes	7-12 minutes	7-12 minutes
Hourly Max Limit	0.1 mg/kg/hr	0.02 mg/kg/hr	1 mCg/kg/hr
Available Concentration	Standard Concentration 1 mg/1mL Concentrated** Concentration 3 mg/mL 25 mg/mL *0.25 mg/mL (dilute** library)*	Standard Concentration 0.5 mg/mL Concentrated** Concentration 2 mg/mL 10 mg/mL *0.1 mg/mL (dilute** library)*	Standard Concentration 25 mCg/mL Concentrated** Concentration 50 mCg/mL *10 mCg/mL (dilute** library)*
***Opioid-Tolerant Patients**. Patients who are *opioid tolerant* (typically receiving oral morphine equivalent of 60 mg/day for ≥ 1 week) may require higher doses. Recommend starting PCA with total 24-hour dosing divided by 24 hours for hourly rate and titrate as needed.			
****Concentrated and Dilute Concentration PCAs.** At BCH initial order must be written by Pain Service. PACT and primary team can modify following initial order. *Consider in patients who may need more concentrated or more dilute solutions. Consider concentrated solution in advance when there is a potential need to escalate PCA rapidly at end-of-life.*			
Escalation of PCA b. Increase *continuous and demand* by 30% for mild, 50% for moderate, 75-100% for severe pain			

Opioid Rotation: Making an equianalgesic opioid conversion[6] (5 Step Process)
1. Assess the pain and side effects to determine if rotation is the best intervention
2. Determine patient's total daily consumption of opioid
3. Set up ratio using data from equianalgesic table and calculate total daily dose of new opioid
4. Modify the calculated dose, generally reducing by 25-50% for incomplete cross-tolerance, guided by the patient-specific situation. Determine new opioid regimen (dose, interval, and rescue dose). Use a second method to confirm correct dose (i.e., colleague or opioid calculator such as on GlobalRPH.com)
5. Implement new dose and monitor patients' response carefully. Liberal access to breakthrough agent is necessary to ensure patient does not experience excess pain during the transition.

Transdermal FentaNYL (TDF)[6] *Use lowest dose possible and titrate based on patient response* See: www.TIRFREMSaccess.com	
Patch Formulations	12 mCg/hr*; 25 mCg/hr; 50 mCg/hr; 75 mCg/hr; 100 mCg/hr **releases 12.5 mCg/hr*
Conversion Factor	Every 2 mg PO morphine/day ⇒ 1 mCg/hr TDF *calculate TDD morphine to determine patch dosing
Considerations	Good choice for chronic pain that is unlikely to fluctuate significantly. **Patients must be taking at least 60mg of oral morphine equivalent daily to start TD patch** Bad choice for patients who are opioid naive, with minimal subQ fat Increased absorption with fevers. Avoid use of heating pad near patch. Do not cut patches. Dispose of carefully to avoid accidental exposure or ingestion
Initiating TD Patch **Takes at least 12 hours to achieve adequate analgesia, max concentration takes up to 36 hours, and 3-6 days to reach steady state*	Oral Immediate Release (IR) Opioid → TDF Apply patch at same time as last dose of ER opioid Continue to provide IR formulations for breakthrough pain as patch takes effect IV Opioid Infusion→ TDF Decrease IV infusion to 50% of the original rate 6hr after patch applied Discontinue IV infusion 12hr after patch applied
Discontinuing TD Patch **It takes 17-24 hours for 50% of FentaNYL to be eliminated from body after patch removal and > 50hours for 90% elimination*	For first 12hr after patch removal, use only IR opioid rescue pain doses 12 hours after patch removal, begin with 50% calculated scheduled opioid regimen 24 hours after patch removal, increase to 100% calculated scheduled opioid regimen
Other Transmucosal Options	Transmucosal lozenge, Effervescent buccal tab, buccal soluble film, Sublingual tab, Sublingual spray, nasal spray

<table>
<tr><th colspan="2">Methadone[7]</th></tr>
<tr><td colspan="2">Racemic mixture of two enantiomers with unique properties:
R- methadone: opioid receptor activity (μ, Δ and K)
S- methadone: NMDA antagonist; reuptake inhibitor of 5- HT, norepinephrine
NMDA antagonism results in decreased opioid tolerance/increased sensitization/increased analgesic effect (relatively lower methadone dose has same effect)</td></tr>
<tr><th colspan="2">**Pharmacokinetics (oral dosing)** **significant variability between individuals**</th></tr>
<tr><td>Bioavailability</td><td>Little first pass hepatic metabolism, >80% bioavailability
High lipophilicity; high mucosal absorption</td></tr>
<tr><td>Metabolism</td><td>Largely by CYP2B6 and CYP3A4
→ *Smoking*: induces CYP2B6 (lowers methadone levels)
→ *Genetics*: Wide range of genotypes
→ *Changes in concomitant medications*: ***check at every visit!***</td></tr>
<tr><td>Elimination</td><td>$t_{1/2}$ is variable, though long (about 22hr)
Biphasic pattern
α-elimination phase (8–12hr): correlates with analgesia duration
β-elimination phase (30–60hr): levels sub-analgesic but prevent withdrawal
No active metabolites</td></tr>
<tr><td>Excretion</td><td>Predominantly in feces
Does not accumulate in renal failure
Not appreciably filtered during hemodialysis</td></tr>
<tr><td>**Analgesic Activity**
both short and long-acting analgesic</td><td>*Long analgesic activity* (approximately 3-6hr with initiation and 8-12hr with repeated dosing)
Onset of analgesia is short (30-60min) → peak effect 2.5-4hr</td></tr>
<tr><th colspan="2">Methadone Prescribing Recommendations</th></tr>
<tr><th>Assess for Risk of QTc prolongation</th><th>Use with Extreme Caution</th></tr>
<tr><td>Structural heart disease
Congenital heart disease
Electrolyte abnormalities
Concomitant *QTC-prolonging* medications: *For a list see crediblemeds.org*</td><td>Congenital QTc syndrome (patient or family)
QTc >500ms
Sole opioid for patients with prognosis <5 days (insufficient time to achieve steady state)</td></tr>
<tr><th>Starting Dose</th><th>Oral Formulations</th></tr>
<tr><td>0.05-0.1mg/kg/dose q8-12 hours PO
0.025-0.05mg/kg/dose q8-12 IV</td><td>5mg/5mL, 10mg/5mL, 10mg/1mL
5mg, 10mg tabs</td></tr>
<tr><th colspan="2">Dosing and Titration</th></tr>
<tr><td colspan="2">Initial dose should not be more than 30-40mg/day
Given time needed to achieve steady state (~5 days) dose should be titrated every 3-5 days
Initial dose increases of methadone should not be more than 10mg per day every 3-5 days
Subsequent increases should be no more than 30% every 3-5 days
Monitor for opioid receptor mediated adverse effects (e.g. sedation, constipation)</td></tr>
<tr><th colspan="2">Monitoring: Based on QT Prolongation Risk and Goals of Care</th></tr>
<tr><td colspan="2">QTc Monitoring: An Approach Based on Guidelines Issued by The American Pain Society
Obtain EKG obtained prior to initiation of methadone (if consistent with goals of care)
Obtain follow up ECGs 2-4 weeks after dose increases, (depending on risk and goals of care)
Risk higher with IV methadone (due to chlorobutanol preservative).
Be aware of concomitant drugs that may potentiate the repolarization caused by methadone.</td></tr>
<tr><td colspan="2">*QTc prolongation: ≥460 milliseconds (ms) for prepubertal children, ≥470ms for pubertal males, and ≥480ms for pubertal females*[8]*</td></tr>
</table>

Methadone[9]	
Selected Drug Interactions (*not comprehensive***)**	
Increase methadone levels	CYP 3A4 inhibitors, ciprofloxacin, isoniazid, diazePAM, clonazePAM, cimetidine, verapamil, dilTIAZem, nefazodone
Decrease methadone levels	CYP3A4 inducers, carBAMazepine, nevirapine, nelfinavir, phenytoin, PHENobarbital, rifAMpin
Prolong QT interval	5-HT3 antagonists, haloperidol, QUEtiapine, OLANZapine, chlorproMAZINE, amitriptyline, desipramine, imipramine, nortriptyline
Increase circulating methadone levels **AND** prolong QT	-azole antifungals, erythromycin, clarithromycin, azithromycin, fluvoxaMINE, PARoxetine, FLUoxetine, sertraline

Opioid Conversion → Methadone[10] *requires expertise* (**CROSS TOLERANCE reduction already accounted for**)		
Not for use to convert from Methadone		
Oral DAILY morphine equivalents	Enteral DAILY methadone dose	Parental DAILY methadone dose
< 50 mg	*See starting dose on page 9* *For infants, see page 31*	
50-100 mg	5-10 mg	3.5-10 mg
101-150 mg	10-20mg	7.5-15 mg
151-200 mg	15-30 mg	10-22 mg
201-300 mg	20-40 mg	15-30 mg
301-400 mg	24-44 mg	18-32mg
>400 mg	30 mg	22-37 mg
Generally, convert to no more than 30mg/day methadone, then titrate upwards as above		

Converting between Methadone IV and Methadone PO
• *Bioavailability of methadone is variable: enteral range is 36%-100% of parental dose* • *Adjust based on estimated absorption.* • *PO to IV: 2:1 conversion is recommended (2:1.5 may also be appropriate)* • *IV to PO: 1:1.25 conversion is recommended (1:1 conversion may also be appropriate)*
Methadone → Oral Morphine
PO methadone to PO morphine: 1:4.7 IV methadone to PO morphine: 1:13.5

Opioid Equianalgesic Doses[6] *Recommend two-clinician verification with opioid conversions prior to placing order with additional confirmation using GlobalRPH.com.*		
Drug	**PO/PR (mg)**	**SubQ/IV (mg)**
Morphine	3	1
OxyCODONE	2	n/a
HYDROmorphone*	0.75	0.15
Methadone	*(see page 10)*	
FentaNYL *(see page 8)*	n/a	0.01 (10 mCg)
Equianalgesic ratios are ***approximate***. The ratios chosen above reflect a consensus drawn from several sources. Other conversions tables exist and may show different ratios. Individual patients may have very different absorption or cross tolerance and ALL opioid conversion procedures should be conducted or overseen by clinicians with experience. *Hydromorphone ratios have been shown to have large interpatient variability.[11]		

Opioid Regulatory Considerations	
Opioid Agreement	To be completed by primary opioid prescriber when prescribing opioids long-term. Separate opioid agreements for DFCI / BCH. Copy opioid agreement and scan into electronic medical record.
MassPAT	**Massachusetts Prescription Awareness Tool** is the online prescription monitoring program in Massachusetts (https://massachusetts.pmpaware.net/login). All clinicians who write controlled substances must register with MassPAT. Checking MassPAT before issuing any prescription for a drug in schedule II or III and before each new benzodiazepine prescription is mandatory.
Naloxone RX	Consider co-prescription order for any patient discharged on opioids (especially long-acting). Typically, Intranasal RX. (4mg:0.1mL).
Discussion of safe opioid practices	Safe storage of opioids Lock box
Documentation	**Document the above in the EMR with every opioid prescription.**

Management of Opioid Side Effects	
Adverse Effect	**Management Considerations**
Constipation	Start with a stimulant + osmotic agent, see constipation section (*see page 24)* For refractory opioid-induced (OI) constipation[12,13] Methylnaltrexone 0.15 mg/kg (max 8-12mg) q48hr subQ Relistor* (PO) 450mg daily (adult dosing) PO PRN, Naloxegol* (Movantik) PO 12.5-25mg daily (adult dosing), Lubiprostone* (Amitiza) PO, Linzess PO **likely to require prior authorization**
Delirium	Assess for coexisting factors (drugs: anticholinergics; metabolic alterations: infection, dehydration, renal, liver, electrolyte, brain metastases) Consider reducing opioid (if possible) or opioid rotation Consider neuroleptic (haloperidol, risperiDONE, OLANZapine, *(see pages 27-28))*
Nausea & vomiting	See N/V section *(pages 21-23)*
Neurotoxicity **Hyperalgesia** **Myoclonus**	Characterized by acute delirium, myoclonus, seizure, hyperalgesia, and hallucinations Rotate opioid, hydration, consider above for myoclonus, consider stimulant for sedation Consider adjuvants (*see page 13-15*) for pain to allow potential opioid reduction; consider ketamine (NMDA blockade, *see page 14*); consider opioid rotation Reduce dose (if possible) or add adjuvant / rotate opioid Increase hydration to enhance clearance of toxic metabolites Consider ClonazePAM 0.25-0.5mg PO TID; LORazepam 0.5-1 mg PO/IV QID; Baclofen 5-10mg PO TID
Pruritus *Highest risk with IV opioids (morphine > hydromorphone > fentanyl)*	Nalbuphine[14] 0.01-0.02 mg/kg (1.5mg) IV q6hr Naloxone (1-2 mCg/kg/hour) continuous IV infusion[15] Antihistamines not effective (opioid induced itching not solely histamine mediated) *No typical outpatient regime*
Respiratory Depression	Opioid antagonists can reverse opioid-induced respiratory depression; however, *they also may reverse analgesic effects* Naloxone should **NOT** be administered for a depressed RR accompanied by normal O2 saturation, or for a patient who is arousable In either of those cases, **reduce** the opioid dose, provide verbal and tactile stimulation, and continue to monitor the patient closely. If naloxone is needed: dilute 0.4 mg (1mL) in 9 mL of NS, and give IV in 1-2mL increments at 2-3 min intervals until response
Sedation	Tolerance typically develops and sedation improves within a few days. What initially appears to be sedation may be catch-up sleep made possible by controlled pain. Hold other less necessary drugs that are CNS depressants Methylphenidate for persistent fatigue in the morning and mid-day *(see page 28)*
Urinary Retention	Consider bladder scan to evaluate for retention Consider crede maneuver, urinary catheter Nalbuphine[16] q6hr IV PRN (0.05-0.1mg/kg/dose) shown to be effective for opioid induced urinary retention Consider bethanechol (0.2 mg/kg, max 10mg, PO q8hr)

Adjuvant or First Line Analgesic Agents[17,18] *See table on page 20 for medications specific for symptoms for SNI population*			
Medication	**Indications**	**Usual Starting Dose & Interval**	**Comments**
Anticonvulsants, Gabapentinoids			
Gabapentin 50mg/1mL; 100mg, 300mg, 400mg caps	Neuropathic Pain	Initial Dose: 2 mg/kg (100 mg) PO TID **OR** 5 mg/kg (250 mg max) PO QHS Increase by 2mg/kg/dose (5-6 mg/kg/day) q2-4 days until effective analgesia reached (often noted at 30-45 mg/kg/day) Max total dose of 50-72 mg/kg/day reached (2400-3600 mg/day) Give **half** of TDD QHS if symptoms occur mostly in evening/overnight	Pre-amputation to reduce post-op phantom pain Side effects experienced (nystagmus, sedation, tremor, ataxia, swelling) Adjust dose for renal dysfunction (CrCl <60mL/min) Younger children (<5 years) may require a 30% higher mg/kg/day dosing, (TDD of 40-60 mg/kg) Titrate more rapidly for severe pain or as tolerated
Pregabalin 20 mg/mL; 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg caps		Day 1-3: 1 mg/kg/dose (50mg max) PO QHS Day 4-6: 1 mg/kg/dose PO q12hr Increase q2-4 days to 3mg/kg/dose PO q12hr (max 6 mg/kg/dose)	Adjust dose for renal dysfunction (CrCl <60mL/min) CrCl 30-60: 150mg BID CrCl 15-30: 75 mg BID CrCl <15: 75mg daily

Converting Gabapentin to Pregabalin[19]

cross-titrating between gabapentin and pregabalin is not necessary. Recommend discontinuing gabapentin and initiating pregabalin with equivalent dosing at next interval

Total daily dose of Gabapentin in mg (pre-switch)	*Total daily dose of Pregabalin in mg (post-switch)*
0-300	*50*
301-450	*75*
451-600	*100*
601-900	*150*
901-1200	*200*
1201-1500	*250*
1501-1800	*300*

For total daily dose of gabapentin > 1800mg;
every additional 300mg of gabapentin = + 50mg pregabalin
(up to max 3600mg gabapentin & max 600mg pregabalin)

Other Antiepileptics to Consider (3rd or 4th line in adult algorithms for neuropathic pain)[20,21]

Valproic Acid, OXcarbazepine, LamoTRIgine, Topiramate

<table>
<tr><th colspan="4">Tricyclic Antidepressants (TCA)</th></tr>
<tr><td>Amitriptyline

10mg, 25mg, 50mg, 75mg, 100mg tabs

Nortriptyline

10mg/5mL;
10mg, 25mg, 50mg, 75mg caps</td><td>Neuropathic Pain</td><td>Day 1-4: 0.2 mg/kg (max 10 mg) PO QHS
Increase q4-5 days by 0.2 mg/kg/day until effective analgesia OR dosing reaches 1 mg/kg/day (max 50 mg/day)
Consider twice daily dosing of 25-30% qAM and 70-75% qPM</td><td>Both have higher rate of side effects with higher doses (including anti-cholinergic)

Side effects: constipation, dry mouth, urinary retention, sedation. (Anticholinergic side effects Amitriptyline > nortriptyline)</td></tr>
<tr><th colspan="4">Selective Norepinephrine Reuptake Inhibitors (SNRI)</th></tr>
<tr><td>DULoxetine

20mg, 30mg, 40mg, 60mg caps</td><td>Neuropathic Pain
Fibromyalgia</td><td>Initial dosing: 30 mg daily for two weeks
Titrating dose: After 2 weeks, increase dose to 60mg daily
If needed, increase by 30mg increments to max 120mg/day (may be divided into BID dosing)</td><td>First line agent for cancer-related peripheral neuropathy
Helpful for patients with comorbid anxiety/depression

Capsule may be opened and sprinkled onto food, though not recommended</td></tr>
<tr><th colspan="4">Topical Agents</th></tr>
<tr><td>Lidocaine patch[22]
(4%)</td><td></td><td>Apply to intact skin over most painful area, may leave in place for up to 18-hr in a 24-hr period, OK to cut</td><td></td></tr>
<tr><td>Topical NSAIDs
[Diclofenac]

1% gel, 3% gel
Patch (for > 6yrs)</td><td>Joint pain</td><td>Gel→ apply using dosing card to measure, 3-4x daily up to 7 days
Patch → apply 1 patch 1-2x daily up to 14 days</td><td>Use lowest effective dose for shortest duration of time
Avoid over open skin or mucous membranes, allow at least one hour before bathing, wash hands immediately after applying</td></tr>
<tr><th colspan="4">N-Methyl-d asparate (NMDA) Antagonists</th></tr>
<tr><td>Ketamine[23-26]

100mg/mL (5mL) use injection for oral doses; Intranasal</td><td>Analgesia; Opioid-sparing effects</td><td>IV infusion: 0.12-0.42 mg/kg/hr (2-7 mCg/kg/min) typically start at 2 mCg/kg/hr and titrate by 1 mCg/kg/min increment</td><td><table><tr><th>Dose (mg/kg)</th><th>Effect</th></tr><tr><td>0.1-0.3</td><td>Analgesia</td></tr><tr><td>0.4-0.6</td><td>Partial dissociated</td></tr><tr><td>> 0.7</td><td>Dissociative</td></tr></table>1:1 conversion ratio</td></tr>
</table>

Alpha-2-adrenergic Agonists			
Dexmedetomidine[27]		0.2-1 mCg/kg/hr IV infusion * Doses as high as 2.5 mCg/kg/hr Infant may need higher infusion rates than older children	**typically done in ICU* *Does not cause respiratory depression.* *May cause hypotension*
CloNIDine 100mCg/mL 0.1mg, 0.2mg tabs TD Patch Dosing: 0.1 mg/24hr 0.2 mg/24hr 0.3 mg/24hr *Patches can be cut to achieve 50mCg*	Neuropathic Pain; Opioid withdrawal	Day 1-3: 0.002 mg/kg (2 mCg/kg) PO QHS (0.1 mg) Day 4-6: 0.002 mg/kg (2 mCg/kg) q12hr Day 7-9: 0.002 mg/kg (2 mCg/kg) q8hr Doses may be increased by 0.002 mg/kg (2 mCg/kg) as tolerated (monitor for hypotension) May titrate more rapidly as tolerated	**Converting from PO → patch** (patch reapplied q7 days) Day 1: Apply patch, give 100% oral dose Day 2: Give 50% oral dose Day 3: Give 25% oral dose Day 4: Discontinue oral dose **Converting from CloNIDine patch→ PO CloNIDine** Remove patch Administer initial oral dose 8 hours later
Corticosteroids			
Dexamethasone[28] 0.5mg/0.5mL; 0.5mg, 1.5mg, 4mg tabs	Dosing for Spinal Cord Compression Increased ICP Bowel obstruction Hepatic capsular distention	1-2 mg/kg (max 10mg) IV load **THEN** 1-1.5mg/kg/day IV divided into q6-12h dosing (max daily dose = 16mg) *Higher maintenance doses for spinal cord compression associated with higher incidence of side effects without greater benefit	
	Dosing for Bone Pain/Edema	0.02-0.03 mg/kg/day in 2-3 divided doses (max daily dose ~10-12mg/day)	
Bisphosphonates			
Pamidronate	Metastatic bone pain, delay of bone metastasis progression, hypercalcemia	0.5mg-1mg/kg IV q4 weeks (>60kg) 90mg IV q4 weeks, may decrease interval to q3 weeks	Reduce dose for renal dysfunction May cause myalgias and fevers
Zolendric Acid		1st time dose: (pts >2 years of age) 0.0125mg/kg/dose Subsequent doses (pts >2 years of age) 0.025-0.05mg/kg/dose 4mg IV q4 weeks, may decrease interval to q3 weeks	
Miscellaneous			
Carbamazepine 20mg/mL; 200mg, 100mg tabs	Trigeminal or glossopharyngeal neuralgia	200-400mg/day in 2-4 divided doses based on formulation. Maintenance 600-800mg/day; max 1200mg/day.[29,30]	Increase overall several weeks in increments of 200mg/day as needed
Loratadine 1 mg/mL; 5 mg/5 mL 10 mg tab	GCSF related bone pain	2-5 years: 5 mg daily ≥6 years: 10 mg daily	Use in conjunction with famotidine[31]

Additional Considerations
Newer considerations for alternative / adjunctive pain strategies include **Lidocaine** and **Mexiletine**. Seek local practice experts, Pain Team at BCH.
Consider interventional approaches with local practice experts, Interventional Pain Team at BCH.

Weaning Guidelines[32-34]

- If drug has been in continuous **use > 5 days**, consider a wean (especially for opioids and benzodiazepines)
- Rule of thumb when weaning any medication is to reduce by 20-30% and observe for breakthrough symptoms or withdrawal symptoms. There is no evidence to support any one weaning strategy, it should be individualized to patient.
- Frequency of weaning steps depends on half-life of drug and how long patient has been on it
- Longer half-life and longer duration of use = slower wean
- Generally, the last step of wean is the starting dose. In some patients, doses below typical starting dose are needed to avoid withdrawal symptoms.
- Patients on benzodiazepines > 3 months or with chronic pain on opioids > 6 months will likely need a VERY SLOW wean (5-10% of original dose per week)

Withdrawal - Symptoms include, (not limited to) anxiety, agitation, dysphoric mood, nausea/vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, insomnia

- **CloNIDine** can be used to mitigate withdrawal symptoms
  - PO 5 mCg/kg/day, divided every 8-12 hours or rounded to nearest ¼ patch size for transdermal dosing (max initial dose 100 mCg/day)

WAT score > 3 indicates likely withdrawal, consider slowing wean.

See BCH guidelines in Lexicomp for dexmedetomidine conversion to clonidine and other weaning guidelines.

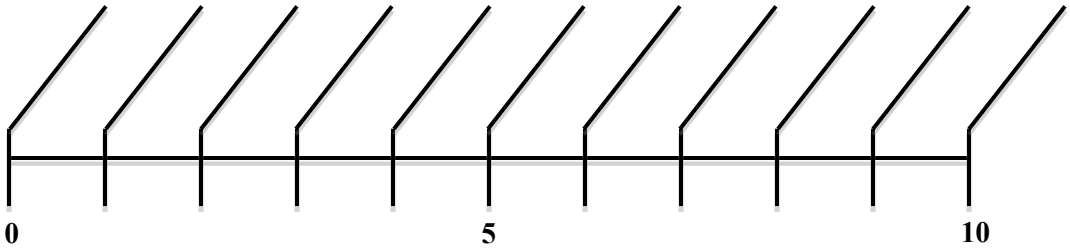
Chronic Pain

- Pain that occurs for more than 3 months, and often involves neuroplastic changes such that pain is no longer nociceptive (and traditional agents for nociceptive pain (eg opioids, anti-inflammatories are less effective)
- Causes include musculoskeletal, visceral, post-surgical, neuropathic, and central pain syndromes
- The goal is pain control and improved function, as opposed to complete pain relief:
  - Elimination of symptoms is often not possible
  - Improved comfort and function is possible and may require re-evaluation of treatment goals
- Approach must be multidisciplinary, including non-pharmacologic, psychological, emotional and pharmacological therapies
- *See page 19* for recommendations on **Interventional Language Strategies**
- *See page 19* for recommendations for screening children with SNI for risk of chronic neuro-pain

Children with Impairment of the Central Nervous System

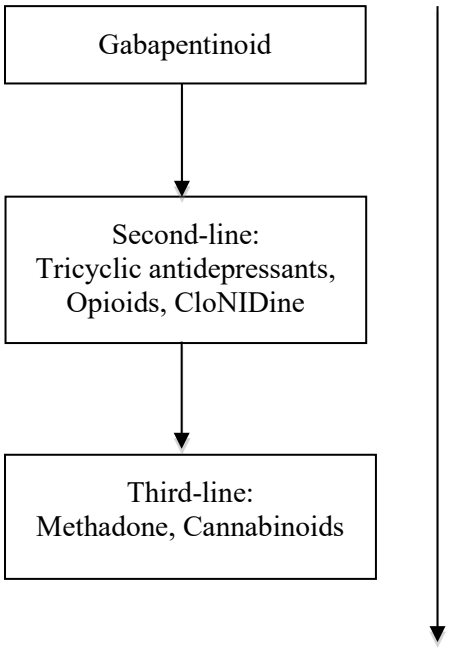
Pain behaviors in children with severe neurological impairment (SNI)
- *Vocalizations*: crying, moaning - *Facial expression*: grimacing, frowning, eyes wide open - *Unable to console*: difficult to calm, not soothed by parent comfort actions - *Interaction*: withdrawn, seeking comfort - *Physiological*: tachycardia, sweating, pale or flushed skin, tears - *Muscle tone*: intermittent stiffening of extremities, clenching of fists, muscle tensing, tremors, back arching - *Movement*: increased from baseline, restless, startles easily, pulls away when touched, twisting
Acute and Post-Surgical Pain Assessment
INRS **R-FLACC**
Evaluation of Pain
- Causes, history, and exam pg e6-e7 of AAP clinical report[35] - Initial tests: Blood (CMP, CBC, lipase), urine (UA/UCx), X-ray or bone scan if fracture suspected, and guided by history or exam (e.g. head imaging for shunt, place longer low profile G-tube if tight against abdomen due to growth) - *Consider* abdominal ultrasound, dental exam if no recent exam

Individualized Numeric Rating Scale (INRS): In the diagram below, write in your child's typical pain behaviors on the line that corresponds to its pain intensity, where 0 = no pain and 10 = worst possible pain (see article for further information)



Screening children with SNI for risk of chronic neuro-pain[36]
1. Does your child have any of the following? - Frequently not calm - Intermittently agitated, irritable, cranky, uncomfortable, without a consistent explanation - Chronic poor sleep - Symptoms that continue after 1 or more interventions for: o Autonomic dysfunction and storms o Spasticity or dystonia o Gastrointestinal reflux disease (GERD) and vomiting o Constipation with discomfort o Pain with feeds, not tolerating tube feeds 2. Review prior testing for sources of pain 3. Review for testable chronic pain sources, such as: - Dental, hip subluxation, chronic dry eyes, renal stones - Note: Some findings can be incidental and not the reason for symptoms 4. Screen for risk of chronic pain due to CNS sources without diagnostic tests - See History from N-PRAT (Neuro-Pain Risk Assessment Tool) below - Use score to guide decision to initiate medication trial

Suggested guidelines for pharmacologic management of chronic neuro-pain[35-38]



History from N-PRAT as guide to start / add Medication

- Pain is Chronic: (*see definition above)*
- Level of disability: GMFCS level 4 to 5 or moderate to profound intellectual disability
- AND 1 or more of the following
  - Episodes with rapid onset, out of the blue
  - Intermittent increase in muscle tone, spasms, movement, posture
  - Autonomic dysfunction features: flushing of skin, sweating, tachycardia, hypertension
  - GI symptoms: pain with feeds, gas and constipation; improvement following flatus and a bowel movement
  - Chronic poor sleep
  - Post-surgical: pain >2 months post-surgery without a source
  - Intractable seizures
  - Planned surgery: gabapentinoids may decrease need for post-surgical opioids and development of postsurgical pain

Chronic Symptom Management Strategies[35] for SNI
- Scheduled medication(s): recurrent episodes that do not respond to typical comfort strategies, and are of significant severity, duration, and frequency (e.g. 3 or more episodes per week or a cycle of daily episodes for 4-7 days q2-4 weeks) - Breakthrough care plan: chronic neuro-symptoms can be decreased with scheduled medications but not cured; breakthrough symptoms can still occur - Lessen distention of the GI tract: causes of chronic neuro pain can decrease the amount of distention that triggers pain signals; assess for excessive calories[36] - Co-morbid problems: review management of other problems
Steps for each medication trial for chronic neuro-pain
- Initiate a gabapentinoid: N-PRAT can guide decision to start - Define goals of treatment: e.g. pain reduction, improved sleep, improved feeding tolerance - Initial trial: 3-4 weeks - Initial sedation: can mean the drug is working - Sedation that persists with good symptom control: decrease other sedating drugs (e.g. benzodiazepine, baclofen) before attributing sedation to gabapentinoid - When to consider a 2nd or 3rd drug: symptoms persist after 1st dose maximized, new sources and co-morbid problems assessed, continue other drugs if adding 2nd or 3rd - Potential for less benefit with 3 or more trials given the inability to eliminate sources due to the impaired CNS; a time to revisit goals of care

Chronic Symptom Management Strategies *continued for* SNI

New breakthrough symptoms at time of good symptom control

- Assess for new pain source: see Acute Pain for evaluation
- Lessen GI tract distention: manage constipation, consider calorie decrease as metabolism may have decreased[36]
- Adjust medication plan when symptoms persist after first steps:
  - Maximize dose of chronic pain medications
  - Initiate 2nd or 3rd drug trial if episodes frequent and prolonged
  - Continue other medications when adding 2nd or 3rd
- Review management of co-morbid problems: GERD, spasticity, dystonia, sleep
- Symptoms can worsen in the hospital and during puberty then improve

Non-Pharmacologic strategies to promote comfort in children with SNI

Comfort strategies	Cuddling, rocking, massage, warm baths, music, adjusting enteral feed rate, venting gastrostomy tube
Positional	Repositioning, supportive seating systems, supportive bedding/mattresses
Sensory	Weighted blankets, vibratory mats and pillows
Integrative	Essential oils, aromatherapy, Reiki, craniosacral therapy, acupressure

Interventional Language Strategies for Neuro-Pain: A Framework for Families

- Neuro-pain is a chronic form of pain due to alterations in the nervous system, often with recurrent episodes of different intensity. It can be improved but not fixed; breakthrough symptoms can still occur, just like breakthrough seizures can occur on treatment.
- There are no tests to confirm neuro-pain. Your son is at risk for this type of pain and has many of the features that occur with this type of pain. As an example, the nerves that send pain signals between the gut and brain are often part of this type of pain, causing gut symptoms in some. I recommend that we try a medication for neuro-pain.
- Muscle spasms and increased movement are common. Everyone tenses when in pain. Your son's brain makes his muscles tense much more when pain occurs. This can result in back arching, stiffening of legs, muscle tremors, and startling in children like your son.
- We will give you a plan to manage breakthrough symptoms. We will update this plan as we learn what helps your son most.
- Treatment will not mask pain from a new cause, such as pain from a bladder infection.
- I wish this was an easy form of pain to treat. This will get better, but I can't promise it will improve as much as we hope with the first drug. We will focus on the hoped-for benefit. If this doesn't occur, we will discuss next steps to make this better.
- I wish I could guarantee that this would be better within a week. For many children, this is a slow process over weeks to several months to figure out the plan that works best. Our team is available when needed. This can be hard with support needed throughout.
- This is complex and confusing; here is a summary of some of the information we discussed:
  - Courageous Parents Network
  - Complex Care Journal (Table 3 of Chronic Pain article)

Management of Neurological Problems in Children with SNI		
Medications	**Initial dose (max starting dose)**	**Comments**
Autonomic Dysfunction / Dysautonomia		
CloNIDine 100mCg/mL, 500mCg/mL; 0.1mg, 0.2mg tabs; 0.1mg, 0.2mg, 0.3mg transdermal patch sizes	Days 1–4: 0.002 mg/kg (2 mCg/kg) PO TID Days 5-8: 0.004 mg/kg (4 mCg/kg) PO TID Option to start with once a day dose to minimize risk of sedation Option to increase: 0.02 mg/kg (20 mCg/kg) per day average dose identified for spasticity[37] Autonomic storm: 0.003-0.006 mg/kg (3-6 mCg/kg) q4hr PRN Sleep: 0.003-0.006 mg/kg (3-6 mCg/kg) nightly	Better tolerated in children unable to stand; eliminates risk of fall from orthostatic hypotension Central-acting alpha-2-adrenergic receptor agonist, reducing sympathetic outflow
Gabapentin 50mg/1mL; 100mg, 300mg, 400mg caps	Higher doses may be beneficial for children with SNI, up to 60-72 mg/kg/day[39-41]	*(see page 13)*
Propranolol 20mg/5mL, 40mg/5mL; 10mg, 40mg tabs	0.2-0.4 mg/kg PO q8hr (20 mg), increase q3-4 days up to 1.6 mg/kg q8hr (80 mg)	Beta-1 adrenergic receptor antagonist
Central Neuropathic Pain / Visceral Hyperalgesia		
Gabapentinoids, Tricyclic Antidepressants: See pages 13-15 for dosing guidelines		
Gabapentin	See Autonomic Dysfunction (*above*) for higher dosing	(*see page 13)*
Insomnia in children with SNI		
Melatonin 2mg, 3mg, 5mg tabs	Higher doses may be beneficial for children with SNI due to altered pathways of arousal/sleep, up to 10-12 mg nightly[42,43]	Natrol™ reportedly has highest purity
Spasticity		
Baclofen 10mg tab	2.5–5 mg PO TID; increase q 3 days by 5–15 mg/day up to a max of 60-80 mg/day	Modulates GABA-B receptors
TiZANidine 4mg tabs	0.04–0.08 mg/kg (4 mg) PO QHS, increase up to 0.16 mg/kg q8hr (max 8-12mg q8hr)	Less experience in younger children *Recommend collaboration w/ neurology & psychiatry*
CloNIDine	*See Autonomic Dysfunction, above*	
DiazePAM 2mg, 5mg tabs	0.03–0.05 mg/kg (2 mg) PO or IV q6-8hr, titrate to effect (max 10 mg)	Not recommended for long term use
Dystonia		
Trihexyphenidyl 2mg/5mL; 2mg, 5mg tabs	0.1-0.2 mg/kg/day in 2 to 3 divided doses; doses as high as 2.6 mg/kg/day in 3 divided doses described in children	Anticholinergic *Recommend collaboration w/ neurology & psychiatry*
CloNIDine	Status dystonicus: 4-6 mCg/kg q4hr PRN[44]	Higher doses for inpatient
Myoclonus		
ClonazePAM 0.1mg/mL; 0.125mg, 0.25mg, & 0.5mg tabs	0.005–0.01 mg/kg PO q8-12hr (0.5 mg), up to 0.2 mg/kg/day	May result in hypersalivation

Management of Neurological Problems *continued for SNI*		
Seizures: acute therapy for prolonged seizure		
LORazepam 2mg/mL; 0.5mg, 1mg, 2mg tabs	0.1 mg/kg (max 4 mg) PO/SL/PR q15 min x 2	Home care plans can be adjusted as goals of care change.
Midazolam 2mg/mL, 5mg/mL, *Intranasal*	0.2 mg/kg SL/IN (max 10 mg) q15 min x 2	
DiazePAM 2.5mg, 5mg, 10mg rectal gel	2–5 years: 0.5 mg/kg q15 minutes x 3 6–11 years: 0.3 mg/kg q15 minutes x 3 > 12 years: 0.2 mg/kg q15 minutes x 3	
END SNI SECTION		

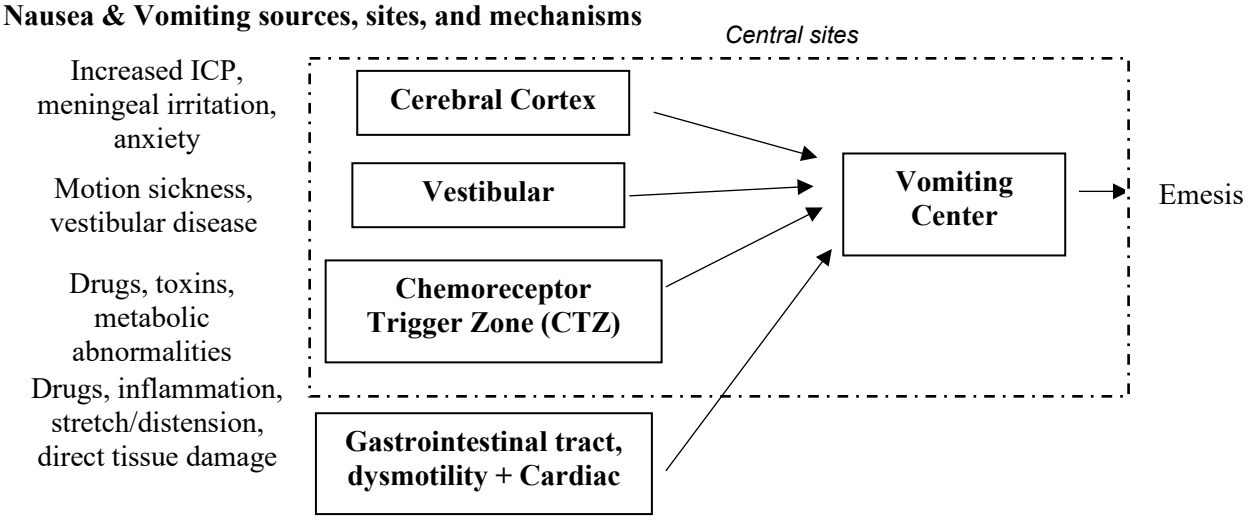
Clinical Framework to Approaching Headaches in PPC

1. Consider differential
2. Collaborate with primary and consulting teams (neurology, neuro-oncology, pain team, psychiatry)
3. Consider role of medication overuse
4. If this is a patient with a brain tumor, recommend providing recommendations as you would for severe cancer pain
   - Consider steroids, celecoxib, +/- opioids

Evaluation and Approach to Nausea & Vomiting

1. Thorough evaluation (H&P), in-depth assessment including other symptoms
2. Reverse or treat underlying cause (if possible)
3. Non-pharmacological approaches
   - Avoid noxious smells, small meals
   - Pericardium 6 (P6) pressure point; SeaBands
   - Ginger, peppermint
   - Aromatherapy (Lemon/citrus, peppermint); scent of isopropyl alcohol helpful to some
4. Pharmacological approach based on underlying mechanism
   - May include multiple mechanisms
   - Use medications targeting different receptors
   - Reassess regularly

Nausea & Vomiting sources, sites, and mechanisms



Sources of Nausea & Vomiting			
Potential Causes	**Receptors / Mechanisms to Target**	**Therapeutic Agents (see below for dosing and administration)**	**Sites**
Medications chemo, opioids, antibiotics, AEDs Metabolic hyponatremia, hypercalcemia, acidosis, uremia Toxins bacteremia, ischemic bowel	Serotonin (5-HT_3) Dopamine (D_2) Neurokinin (NK_1)	*Serotonin antagonists* (Ondansetron, Granisetron) *Butyrophenones* (Haloperidol, Droperidol) *Atypical antipsychotic* (OLANZapine) *NK_1 antagonists* (Aprepitant)	Chemoreceptor Trigger Zone (CTZ) *Floor of fourth ventricle, at blood brain barrier*
Disorders of the vestibular nucleus and CN VIII	Histamine (H_1) Acetylcholine (Ach)	*Antihistamines* (DiphenhydrAMINE) *Anticholinergics* (Scopolamine, meclizine)	Vestibular
Mechanism is unclear	Histamine (H_1) Acetylcholine (Ach)	*Anticholinergics* (Scopolamine)	Vomiting Center (VC) *Final common pathway*
	Serotonin	*$5HT_2$ antagonists* (Cyproheptadine)	
Increased intracranial pressure, tumor, infection	Stimulation of the VC	Corticosteroids	Meningeal Mechanoreceptors
Anxiety	Stimulation of CTZ and VC	Relaxation techniques, Benzodiazepines, Cannabinoid agents	Cortex
Acid reflux		*H2-Blocker (famotidine)*, *Proton pump inhibitors* (omeprazole)	
Dysmotility		*Prokinetic* (metoclopramide), erythromycin *Treat constipation*	

Medications for Nausea/Vomiting/Retching (receptor blocking properties indicated)		
Medication Formulation	**Dosing and route**	**Comments**
$5HT_2$ and $5HT_3$ Serotonin Antagonists		
Ondansetron 4 mg/5 mL; 4mg, 8mg tabs	0.15 mg/kg PO/IV q8hr (4-8 mg; 24mg/day max)	May cause constipation, headache Not effective treatment of delayed CINV
Granisetron 1 mg tab; 3.1mg/24hr patch	40 mCg/kg PO/IV q12-24hr (daily doing for <6 months, otherwise q12hr dosing)	
Atypical Neuroleptic		
OLANZapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20 mg tabs	1.25-2.5mg PO daily, increase if needed, up to 20mg daily	Targets D_2, $5HT_2$, $5HT_3$, H_1; treatment of delayed CINV; also helpful with insomnia

Medications for Nausea/Vomiting/Retching (receptor blocking properties indicated) *continued*		
Medication / Formulation	**Dosing and route**	**Comments**
Dopamine Antagonists (D_2)		
Metoclopramide 5mg/5 mL; 5mg, 10mg tabs	1 mg/kg/dose IV prior to chemotherapy, then 0.0375 mg/kg/dose PO/IV q6hr	Higher doses for CINV; risk of EPS/NMS → *administer with diphenhydrAMINE; c*an also be helpful in dysmotility
Haloperidol 2mg/mL; 0.5mg, 1mg, 2mg tabs	0.01-0.02 mg/kg PO q8hr PRN (0.5-1 mg)	Risk of EPS
Anticholinergic		
Scopolamine 1.5mg TD patch	>age 12: 1.5mg by transdermal patch q72hr	
Neurokinin-receptor Antagonists		
Aprepitant 40mg, 80mg, 125mg tabs *20 mg/ml susp can be made by pharmacy*	>6 months: 3 mg/kg PO (max 125 mg) on day1, then 2 mg/kg q day (max 80mg) Adolescents: 125 mg PO 1hr prior to chemo, then 80mg q day for 2 days	IV form = fosaprepitant *Check with oncology pharmacy for dosing and interactions*[45]
Corticosteroids		
Dexamethasone 0.5mg/5 mL, 1mg/1mL tabs	0.1 mg/kg PO/IV q6hr (max 16 mg/day)	Best for gut wall edema; Can cross BBB. For patients with leukemia or brain tumor discuss first with primary team
Miscellaneous		
LORazepam 2mg/mL; 0.5mg, 1mg, 2mg tabs	0.02-0.05 mg/kg PO/SL/IV/subQ q6hr, PRN (1-2 mg)	Use for anticipatory nausea
Dronabinol 2.5mg, 5mg, 10mg caps Syndros 5mg/1mL	0.05-0.1 mg/kg PO q6-12hr (2.5-5 mg) May increase if tolerated to max of 10mg bid Typically recommend use in ages > 6 years old	Cannabinoid – THC; avoid late PM dose (vivid dreams)

Abbreviations: CINV=chemotherapy-induced nausea and vomiting, EPS= extrapyramidal symptoms, NMS = neuromalignant syndrome, BBB= blood brain barrier

Anorexia/Weight Loss		
Medication Name	**Dosing and route**	**Comments**
Dronabinol 2.5mg, 5mg, 10mg caps Syndros 5mg/1mL	0.05-0.1 mg/kg PO q6-12hr (2.5-5 mg) May increase if tolerated to max of 10mg BID	Late afternoon/evening doses associated with colorful dreams (may be distressing)
Cyproheptadine 2mg/5 mL; 4mg tab	≥ 2 years: 0.25mg/kg/day divided twice daily; ≤ 6 years: 12mg/day max; ages 7-14: 16mg/day max; >15 years: 32mg/day max	May cause sedation, start dose low and escalate slowly

Constipation *(see management of opioid side effects page 12)*		
**** Mush (osmotic) + push (stimulant) + whoosh (enema)****		
Polyethylene Glycol (osmotic) 17gm/packet (or scoop)	0.7-1.5 gm/kg q day (8.5 – 17 g q day)	Most effective given as 'bolus' dose (not sipped over long period)
Lactulose (osmotic) 10gm/15 mL	15-30 mL PO bid or 5-10 mL q2hr until stool	Also used for hyperammonemia; may cause cramping
Milk of Magnesia (osmotic) 400mg/mL	2-6 yrs: 400-1200 mg/day (single or divided doses) 6-12 yrs: 1200 -2400 mg/day >12 years and adolescents: 2400-4800/day	Best if taken with 8oz water
Bisacodyl (stimulant) 5mg tab; 10mg supp	3-10 yrs: 5 mg q day 10-12 yrs: 5-10 mg q day >12 yrs and adolescents: 5-15 mg q day	Tab should not be crushed or chewed
Senna (stimulant) 8.8mg/5 mL; 8.6mg, 15mg tabs; Sprinkles; 10mg supp	2-6 yrs: 2.5-3.75 mL q day; (1/2 tab q day) >6-12 yrs: 5 – 7.5 mL q day; (1 tab/day) >12 years and adolescents: 10-15mL q day; (2 tab/day)	Also available in combination with docusate; sprinkles may be eaten plain, mixed with liquids such as milk to make a drink, or sprinkled on food
Sodium phosphate (enema) Fleet®	1 PR every other day as needed	Risk of electrolyte disturbances, caution in patients with cardiac/renal disease; avoid in immunocompromised patients
Glycerin suppository	1 PR daily Pediatric supp for children <6 Adult supp for children >6	Avoid rectal medication administration in immunocompromised patients
Mu receptor antagonists (opioid-induced constipation) **See page 12 for opioid induced constipation**		
Methylnaltrexone	0.15 mg/kg (max 8-12 mg) q48hr IV/subQ[12]	Subsequent doses (no more than every 24 hours) may be needed
Naloxone[46, 47]	0.25-2 mCg/kg/hr IV continuous infusion	Doses over 2 mCg/kg/hr may reverse systemic opioid effects
Naloxegol[48] (pegylated form of naloxone) 12.5mg, 25mg tabs	25 mg PO q day If not tolerated, reduce dose to 12.5 mg q day	Take 1 hour before or 2 hours after meals; interacts with -azoles
Intestinal Motility		
Erythromycin 200mg/5 mL	2-5 mg/kg PO QID (max 250 mg per dose)	Risk of QTc prolongation with other meds; may cause nausea
Metoclopramide 5mg/5 mL; 5mg, 10mg tabs	Prokinetic: 0.1-0.2 mg/kg PO/IV q6hr (5-10 mg)	Do not need diphenhydrAMINE for EPS with this dose
Gastric Accommodation		
Cyproheptadine 2mg/5 mL; 4mg tab	0.08 mg/kg PO TID (4 mg) If no benefit in 5 days, increase each dose by 0.04-0.08 mg/kg	May cause sedation, start dose low and escalate slowly
Bowel Obstruction		
Octreotide	0.001-0.002 mg/kg (1-2 mCg/kg)subQ, IV q8hr **OR** 0.003-0.006 mg/kg/day (3-6 mCg/kg/day) continuous	Concern for gut ischemia; initiated in ICU unless DNR order in place.

Evaluation and Approach to Diarrhea

1. Thorough evaluation (H&P), in-depth assessment including other symptoms
2. Reverse or treat underlying cause (if possible)
   - *Potential causes*: malabsorption (e.g. short gut), infection, bacterial overgrowth, medications (e.g. antibiotics, magnesium, laxatives), radiation therapy, constipation with overflow/leakage
3. Non-pharmacological approaches
   - Diet: bland, no dairy, added fiber to increase stool bulk
   - Barrier creams to protect skin
4. Pharmacological approach based on underlying mechanism
   - Loperamide (non-absorbable opioid that directly reduces intestinal motility): discontinue when no diarrhea for 12 hours; for radiation-induced diarrhea, continue for the duration of radiation
   - Lomotil
   - Low dose opioid, consider deodorized tincture of opium
   - Octreotide – for severe diarrhea, especially if bleeding; reduces cramping and output *(see page 24)*
   - Special cases:
     - Irinotecan acute diarrhea (cholinergic mechanism): Atropine
     - Irinotecan delayed diarrhea (direct epithelia toxicity): Antibiotics (cefixime), activated charcoal

Evaluation and Approach to Itching

1. Thorough evaluation (H&P), in-depth assessment including other symptoms
2. Reverse or treat underlying cause (if possible)
   - *Potential causes*: dermatologic (e.g. irritation), immunologic (e.g. allergy), drug effect (e.g. opioids), other systemic disease (lymphoma, iron deficiency, liver or renal failure), psychogenic
3. Non-pharmacological approaches (*keep cool, keep skin hydrated, avoid irritants*)
   - Emollients to reduce xerosis
   - Avoid hot baths/showers
   - Oatmeal baths, cooling agents (e.g. Calamine, Sarna™)
   - Cold packs to soothe skin
   - Address pain, boredom, or anxiety, which can worsen itch
4. Pharmacological approach based on underlying mechanism
   - Antihistamines if associated histamine release (diphenhydrAMINE, hydroxyZINE, doxepin for refractory cases)
   - Topical steroids for inflammation (ointment best, if severe consider systemic)
   - Ondansetron (*see page 22)*
   - Aprepitant[49] (cancer biologics, lymphoma) (*see page 23)*
   - Special cases:
     - Cholestatic pruritis: bile duct stenting, cholestyramine, ondansetron, naloxone, naltrexone
     - Uremic pruritis: gabapentinoid, aprepitant, paroxetine

Evaluation and Approach to Respiratory Symptoms

1. Thorough evaluation (H&P), in-depth assessment including other symptoms
2. Reverse or treat underlying cause (if possible)
3. Non-pharmacological approaches

Dyspnea

- Air circulation and fan
- Breathing training
- Relaxation and self-hypnosis
- Occupational and physical therapy
- Acupuncture and acupressure
- Music therapy
- Modification of activity
- Noninvasive positive pressure ventilation

Secretions

- Optimize positioning
- Provide gentle suction
- Reduction of fluid intake

4. Pharmacological approach based on underlying mechanism
   - Reassess regularly

Respiratory Symptoms		
Medication Formulation	**Usual Starting Dose & Interval**	**Comments**
Dyspnea		
Morphine (or opioid equivalent) 10mg/5mL 20mg/1mL 15mg, 30mg tabs	0.05-0.1 mg/kg PO or 0.015-0.03 mg/kg IV/subQ q3-4hr PRN (5 mg PO, 2.5 mg IV) (or other opioids at equivalent dose)	Typical starting dose 25-30% of starting dose for pain medication
LORazepam 2mg/mL; 0.5mg, 1mg, 2mg tabs	0.02-0.05 mg/kg PO/SL/IV/subQ q4-6hr PRN (max 2 mg)	DiazePAM and ClonazePAM may increase secretions
Oxygen	*Only helpful if patient is hypoxemic, otherwise recommend handheld fan directly to face (trigeminal nerve) to improve airflow*	
Secretions		
Ipratropium	250-500 mCg nebulization/MDI q4-6hr PRN	
Glycopyrrolate 0.2mg/1mL; 1mg, 2mg tabs	40-100 mCg/kg/dose PO q6-8hr50 4-10 mCg/kg/dose IV q4hr	Does not cross BBB = less CNS toxicity and side effects
Atropine[51] 1% ophthalmic drops used sublingually	Initial: 1-2 drops sublingually q 2-4hrs Usual dose range: 2 to 4 drops sublingually q 2-4hrs	
Scopolamine Patch (HyoSCINE)	Adolescents: 1.5 mg transdermal patch q72hr	Takes 24 hours to reach steady state; for acute symptoms other drugs should be used
HyosCYAamine 0.125mg/1 mL; 125mCg tablet (SL)	0.125 mg/1 mL solution 3-4 kg 4 drops PO q4hrs PRN 10 kg 8 drops PO q4hrs PRN 50 kg 1 mL (0.125 mg) PO q4hrs PRN	0.125 mg/5 mL elixir also available

Evaluation and Approach to Mood & Sleep Disturbances
It can be difficult to distinguish anxiety, agitation (unpleasant state of arousal), and delirium (fluctuating disturbance of consciousness with acute onset over hours to days). **Consider sources with similar features**: pain, impaired sleep, depression, metabolic disturbances, medication reactions, and progression of a neurodegenerative condition. Children with neurological impairment (NI) of the CNS can have a number of problems that result in agitation and irritability (neuropathic pain, visceral hyperalgesia, dysautonomia, muscle spasms). *See pages 17-20* for symptom treatment guidelines and suggestions in children with SNI.
1. Thorough evaluation (H&P), in-depth assessment including other symptoms 2. Reverse or treat underlying cause (if possible) 3. Non-pharmacological approaches - Close collaboration with psychosocial provider & psychiatry. Consider psychotherapy, hypnotherapy, and/or cognitive behavioral therapy - Create schedule/routine - Provide proper day/ night orientation o Remind the child of where he is and what time of day it is. o Keep lights on and window shades open during day/ off and closed at night. o Encourage the child to be out of bed during the day. o Turn screens off at night - Provide familiar and comforting items to the child (toys, blankets, music). - Provide glasses or hearing aids if needed 4. Pharmacological approach based on underlying mechanism - Reassess regularly

Mood & Sleep Disturbances		
Medication Formulation	**Usual Starting Dose & Interval**	**Comment**
Anxiety		
LORazepam 2mg/mL; 0.5mg, 1mg, 2mg tabs	0.02-0.05 mg/kg PO/SL/IV/subQ q6hr PRN (1-2 mg)	May worsen delirium
ClonazePAM 0.1mg/mL; 0.125mg, 0.25mg, & 0.5mg tabs	0.005-0.01 mg/kg PO q8-12hr (up to 0.25-0.5mg/day)	*Consider collaboration with psychiatry*
Agitation, Delirium		
Haloperidol 2 mg/mL; 0.5mg, 1mg, 2mg tabs	0.01-0.02 mg/kg IV*/PO q8hr PRN (0.5-1 mg) For acute agitation: 0.025-0.05 mg/kg PO/IV, may repeat 0.025 mg/kg in one-hour PRN	IV side effects typically worse than PO; *IV administration limited to ICU unless DNR order in place Risk of QTc prolongation with other medications
RisperiDONE 1mg/1mL; 0.25mg, 0.5mg, 1mg tabs	0.25-0.5mg PO QHS or divided, titrate every 1-2 days, (max 3mg total/day)	Consider as short-term therapy with steroid induced behavior[52]

<table>
<tr><th colspan="3">Mood & Sleep Disturbances continued</th></tr>
<tr><td colspan="3">Anxiety, Agitation, Delirium, Insomnia (if insomnia related to anxiety, agitation, delirium)</td></tr>
<tr><td>OLANZapine
2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20 mg tabs. ODT not available in 2.5mg or 7.5mg</td><td>1.25mg-2.5mg PO daily, increase weekly if needed, up to 20mg daily</td><td>Not available IV</td></tr>
<tr><td>QUEtiapine
25mg, 50mg, 100mg, 200mg tabs</td><td>25mg BID increase daily by 25 mg/dose, (titrate as necessary to 450mg/day)
ER 50mg, 150mg tabs</td><td></td></tr>
<tr><th colspan="3">Mood & Sleep Disturbances… related to steroid use</th></tr>
<tr><td>Hydrocortisone[53]</td><td colspan="2">Physiologic dose (10 mg/m^2/d) while receiving steroid (dexamethasone) for steroid induced insomnia</td></tr>
<tr><th colspan="3">Insomnia</th></tr>
<tr><td>Melatonin
2mg, 3mg, 5mg tabs</td><td>1mg in infants
2-3mg PO QHS may increase to 6mg
Whether to exceed physiologic dosing is debatable</td><td>Common side effects include nightmares and headaches; Natrol™ reportedly has highest purity</td></tr>
<tr><td>TraZODone
50mg, 100mg, 150mg tabs</td><td>0.75-1 mg/kg PO QHS (25-50 mg), increase every 1-2 weeks up to 150mg</td><td></td></tr>
<tr><td>CloNIDine
100mCg/mL, 500mCg/mL; 0.1mg, 0.2mg tabs; 0.1mg, 0.2mg, 0.3mg transdermal patch sizes</td><td>0.002 mg/kg (2 mCg/kg) PO QHS (0.1 mg), increase by 0.002 mg/kg (2 mCg/kg) PO QHS if needed, (max 0.008 mg/kg = 8 mCg/kg QHS) (0.4 mg)</td><td></td></tr>
<tr><td>Zolpidem
5mg, 10mg tabs</td><td>Children <17 years limited data start at 0.25 mg/kg at bedtime; (max 10 mg/dose)
>18 years 5 mg QHS for females 5-10mg QHS for males; (max 10mg/daily)
Extended release 6.25mg Female and 6.25-12.5mg in Males[54]</td><td>Recommend avoiding driving the day after use
Available in immediate and extended release</td></tr>
<tr><th colspan="3">Fatigue</th></tr>
<tr><td>Methylphenidate[55]
5 mg/5 mL,
10 mg/5 mL
5mg, 10mg tabs
Chewable: 2.5mg, 5mg, 10mg tabs
Daytrana TD patch</td><td>0.05-0.1 mg/kg q am and q noon (initial dose is 2.5-5 mg) scheduled or use PRN for directed therapy. May increase based on response by 2.5-5 mg every 1-3 days up to 20 mg twice daily
<table>
<tr><th>Patch Size Daytrana™ (mg/9 hour)</th><th>Immediate Release (mg/day)</th></tr>
<tr><td>15</td><td>22.5</td></tr>
<tr><td>20</td><td>30</td></tr>
<tr><td>30</td><td>45</td></tr>
</table></td><td>Duration of action 1-4 hours; give 30 minutes before desired effect (and avoid 6 hours before bedtime to avoid insomnia).
Rapid t1/2 permits relatively rapid upwards titration of dose, as needed.</td></tr>
</table>

Depression[56,57] *Close collaboration with psychosocial provider & psychiatry.*		
Medication Formulation	**Usual Starting Dose & Interval**	**Comments**
Psychostimulants		
Methylphenidate 5 mg/5 mL, 10 mg/5 mL 5mg, 10mg tabs Chewable: 2.5mg, 5mg, 10mg tabs Daytrana TD patch	2.5-5 mg before breakfast or twice daily before breakfast and lunch; may increase based on response by 2.5-5 mg every 1-3 days up to 20 mg twice daily	Helps mood & fatigue associated with opioid use, psychomotor slowing, & cognitive impairment within 24-48 hours Consider use for depression as monotherapy at the end of life, otherwise consider use as adjunct therapy until antidepressant effective Improves analgesia of opioids Use with caution in individuals with history of significant arrhythmia, Tourette's/tics, mania
Selective Serotonin Reuptake Inhibitor (SSRI)		
Escitalopram 5mg/5 mL; 5mg, 10mg, 20mg tabs	Children >12 yrs 5-10 mg daily *FDA indication for pediatric depression & few drug interactions*	Assess for suicidal ideation given black box warning Consider drug-drug interactions (such as serotonin syndrome or prolonged QTc)) Because they lack anticholinergic effects, SSRIs are preferred for patients with slowed intestinal motility or urinary retention Dose-related side effects common (headache, jitteriness, agitation, sexual dysfunction, diarrhea, nausea, and insomnia) & may subside after 4-7 days
Citalopram 10 mg/5 mL; 10mg, 20mg tabs	5-10 mg daily; may be increased 5mg/day q2 weeks up to 20-40 mg/day	
Selective Norepinephrine Reuptake Inhibitors (SNRI)		
DULoxetine 20mg, 30mg, 40mg, 60mg caps	Children > 7 years old 20-40 mg daily; may be increased 20mg/day q2wks up to 60 mg/day	Also helpful with chronic pain *(see page 14)*
Tetracyclic Antidepressants (TeCA)		
Mirtazapine 15mg, 30mg tabs (available as dissolving tab)	7.5mg QHS; may be increased 15mg/day weekly up to 45 mg/day	Anti-emetic & few drug interactions; side effects sedation & weight gain; sedating at lower doses and activating at higher doses

Significant Toxicity Syndromes		
The most common medication categories to consider include: antidopaminergic (neuroleptics) and SSRIs, paradoxical reactions possible with anticholinergics, benzodiazepines, and antihistamines ***Consider using the Lexicomp Drug Interactions Tool***		
Category	**Associated features**	**Potential causes** (partial list: drugs commonly implicated)
Serotonin syndrome	tachycardia, hypertension, hyperthermia, diaphoresis, mydriasis, diarrhea, hyperreflexia, clonus, agitation, and rigidity	selective serotonin reuptake inhibitors (SSRIs); other drugs, often when used in combination: traMADol, FentaNYL, traZODone, risperiDONE, linezolid, ondansetron, metoclopramide
Neuroleptic malignant syndrome	extrapyramidal effects, muscle rigidity, autonomic dysfunction, hyperthermia, altered mental status	most commonly caused by dopamine antagonists (metoclopramide, neuroleptics), abrupt stop of anticholinergics
Tardive dyskinesia, Dystonia	abnormal movement and posturing, agitation	dopamine antagonists (metoclopramide, haloperidol, risperiDONE)
Akathisia (unpleasant state of motor restlessness)	restlessness, distress, tension and discomfort	dopamine antagonists, TCAs, SSRIs, withdrawal from opioids, paradoxical reactions

Special Considerations for Neonates and Infants < 6 Months of Age
Assessment - Identify and treat underlying etiology of the symptom (if possible). - Use validated neonatal pain scale. (e.g., Neonatal, Pain, Agitation, and Sedation Scale (N-PASS)[58]
Non-Pharmacological Strategies - Reduce painful procedures and unnecessary stimulation. - Encourage swaddling, facilitated tuck, skin-to-skin contact, breastfeeding, and non-nutritive sucking. - Promote a calm, low-stimulation environment with dim lights, lateral positioning, supportive bedding, and familiar sounds. - Consider integrative therapies, such as massage, healing touch,[59] and music therapy.[60]
Physiological Considerations - Glomerular filtration rate (GFR) at birth is reduced by more than 50% of adult levels and increases after two weeks. Effects of low GFR (delayed drug clearance, prolonged half-lives) is more pronounced in preterm infants. Adult levels of GFR are reached around 2 years of age. - Hepatic drug-metabolizing capacity, including the cytochrome P450 system, is reduced in newborns, particularly in preterm infants, and reaches adult levels around 1-2 months of age.
Pharmacological Precautions - NSAIDs are not recommended in infants <6 months due to significant adverse effects, including decreased GFR, platelet dysfunction, and GI complications. - Use opioids with caution in preterm infants and neonates given higher risk of respiratory depression due to immature response to hypoxia and hypercarbia. - Sucrose with non-pharmacological intervention is more effective than sucrose alone. - Gabapentin can be considered for chronic agitation, irritability, and movement disorders. Its use may facilitate weaning from sedative medications.[61] - Midazolam is not recommended in infants under 35 weeks due to higher risk of desaturation, hypotension, and decreased cerebral blood flow, myoclonus, and worse neurologic outcomes. - Dexmedetomidine is not recommended in infants under 35 weeks due to risk of local cerebral vasoconstriction.[62,63] Clearance is longer in premature infants, and lower doses should be used. - Ketamine use is limited to invasive procedures, though may be considered to treat pain and agitation at the EOL in opioid exposed patients.

Medication Dosing Considerations

Dosing and medication route is similar to other pediatric patients with the following exceptions and previous pharmacological considerations.

Medication	Dosing Considerations
Acetaminophen	Max dose of 40 mg/kg/day for 28-32 weeks PMA 60 mg/kg/day for >32 weeks PMA 75 mg/kg/day >40 weeks PMA
Fentanyl, *Intranasal*	1.5-2 mCg/kg divided between each nostril q30 minutes PRN dyspnea
Gabapentin [61,64]	Start at 2.5–5 mg/kg/day PO at night. Increase dose and interval every 3 to 5 days to a max dose of 35 mg/kg/day q8H
Methadone	0.05 mg/kg PO q24 hours Very long half-life (up to 16-25 hrs) in neonates
Midazolam, *Intranasal*	0.2 mg/kg q30 minutes PRN agitation
Morphine	Use lower initial dosing: Start with 25-50% of the standard pediatric doses and up to 75% on non-ventilated patients
Sucrose	0.1-1 mL/dose Buccal/Lingual every 2 min

IV, intravenous; SC, Subcutaneous; PO, per oral; IN, intranasal; PR, per rectum; PMA, post menstrual age

For further guidance for end-of-life care for infants and neonates please see pages 32-33

PC Approach to Managing Escalating Symptoms at End-of-Life [65,66]

Must have an understanding of patient & family goals prior to escalation of medications

Consider the following interventions in all patients	**Specific considerations for children with sensory neural impairment**
Tailor medications and interventions so they are consistent with family goals Discussion of labs &/or diagnostic procedures, VS monitoring and respiratory support (eg may be weaned) Consider holding feeds and/or fluids for the following: - Acute ileus presenting w/ abdominal distention and pain - Peripheral edema - Severe pulmonary congestion	*Tailor medications and respiratory therapies so they are consistent with family goals.* Metabolism declines in the months preceding EOL Consider a reduction of feeds and fluids IF any of the following are noted: - Irritability and pain without a clear source and not responding to adjustments in medications - Escalating respiratory symptoms and secretions - Persistent emesis and feeding tolerance *Reduce by 30% or greater as initial trial, adjust further as needed* Continue medications for seizures, spasticity, and pain

Other Considerations

- Focus on what WILL be done to care for the child
- Consider touchpoints with team, bedside nurse, interdisciplinary team
- Determine most appropriate administration route for patient (oral, IV, TD, subQ)
- Consider adjuvants (e.g., NSAIDs, benzodiazepine, corticosteroids, ketamine)
- Use the term "discontinue" versus "withdrawal"
- Remember other distress (e.g. psychosocial, spiritual) can aggravate symptoms

Rapid Opioid Escalation

<u>If patient is on PCA:</u> → give loading dose 10% of total opioids from preceding 2 hours AND increase PCA/NCA settings

<u>If patient NOT on PCA:</u> → start PCA/NCA and give loading dose

- If symptoms recur, increase PCA dose and continuous by 30%-50% for moderate symptoms, 50-100% for severe symptoms
- Continue opioid titration until symptoms relieved
- No <u>MAX</u> dose for EOL symptoms.

Opioid Rotations

Inadequate analgesia at EOL usually requires dose escalation, not opioid rotation. Consider adding additional analgesics such as methadone or adjunctive therapies
If the patient has significant opioid adverse effects **<u>with</u>** adequate pain control, reduce the equianalgesic dose of the new opioid by 25-50%
If the patient has significant opioid adverse effects **<u>without</u>** adequate pain control, rotate opioid without a reduction in the equianalgesic dose

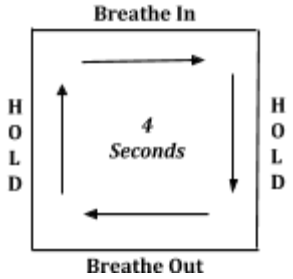
Frequently Used Medications at the End-of-Life (In-patient and/or Hospice Care) ***For home hospice care, contact hospice agency for medications on formulary.***		
Symptom	**Medication** (Hospice formulation)	**Dosing**
Pain	**Morphine** (20mg/mL) *PO/SubQ/SL/IV*	*Pain dosing depends on patients' prior opioid needs* (*See page 6 for initial starting doses)*
Dyspnea	**Morphine**	30-50% pain dosing for opioid naïve patient (*See page 26 for initial starting doses)*
	if worsened by anxiety **LORazepam** (2mg/mL) *PO/SubQ/SL/IV*	0.05-0.1 mg/kg q4h (max 2mg)
Agitation, delirium (nausea)	**Haloperidol** (2mg/mL) *PO/SubQ/SL/IV*	0.01-0.02 mg/kg q8hr PRN (0.5-1 mg) (max 2mg) For acute agitation: 0.025-0.05 mg/kg, may repeat 0.025 mg/kg every hour PRN For agitation/delirium, reduce anticholinergics
Bleeding / hemorrhage	**Aminocaproic Acid** Oral/IV/Topical **Tranexamic Acid** Oral/IV	Apply topically to bleeding (i.e. gums, nose). Oral/IV 100-200mg/kg load, then 100mg/kg/dose q6hr, (max daily dose 30g) 12-25mg/kg/dose PO or 10mg/kg/dose IV up to QID *for epistaxis consider Oxymetazoline (Afrin)*
Secretions	**Atropine** 1% ophthalmic solution or IV formulation to be used SubLingually (SL)	1-2 drops SL q4-6hr PRN
Seizures	**Lorazepam** (2mg/mL) PO/SubQ/SL/IV	0.1 mg/kg/g SL/IV, may repeat dose in 5-10min (max 4mg)
	DiazePAM Rectal	2.5, 5, 10mg rectal gel 2–5 years: 0.5 mg/kg q15 minutes x 3 6–11 years: 0.3 mg/kg q15 minutes x 3 > 12 years: 0.2 mg/kg q15 minutes x 3
	Midazolam Intranasal	<50kg: 5mg >50kg: 10mg
	PHENobarbital PO/IV/subQ/PR	**Maintenance dosing:** Infants: 5 mg/kg/day in 1-2 divided doses 1-5 years 6-8 mg/kg/day in 1-2 divided doses 5-12 years 4-6 mg/kg/day in 1-2 divided doses >12 years 1-3 mg/kg/day in 1-2 divided doses **For terminal seizures:** 15-20mg/kg load, followed by maintenance dose

Palliative Sedation *Used for refractory and distressing symptoms, usually in patients with very limited prognosis.* *Requires close collaboration with family, primary teams, Pain Service (if inpatient) or hospice team* ***Refer to Boston Children's Hospital Palliative Sedation Reference***	
Medication	**Considerations**
Midazolam	Midazolam enhances inhibition at GABA-A receptor Anxiolysis, seizure management, sedation Rapid on/off activity, helpful for respite sedation
PHENobarbital	Phenobarbital enhances inhibition at GABA-A receptor Seizure management, sedation
PENTobarbital	Requires a dedicated lumen Continuous infusion is to be started concurrently with the initial loading dose Slower on/off activity

Alternative Routes to Administration[67]		
Route	**Medication**	**Comments**
Subcutaneous (SubQ)	Most medications can be given subQ, with a 1:1 (IV:SubQ)	
Rectal (PR)	Consult hospice or inpatient pharmacy to convert medication to rectal administration.	

Integrative Medicine/Non-Pharmacologic Symptom Management Strategies[68]

Breathing: Breathing exercises can help us to focus on our breath while calming our nervous system. *Exercise: "Square Breathing"- Complete each step for 4 seconds. If helpful, you can trace the square edges with your finger with each step. Get creative, try with different shapes!*



Helpful scents/ Aromatherapy:[69] Essential Oils are plant-based compounds which can be inhaled (using a "scent stick") to help with various symptoms, here are five common scents:

	Pain	Nausea	Insomnia	Fatigue	Anxiety
Lavender	✦		✦		✦
Sweet Orange			✦		✦
Lemon		✦		✦	
Peppermint	✦	✦		✦	
Grapefruit		✦		✦	✦

Meditation / Guided Imagery: Meditation and guided imagery can be helpful with calming your nervous system and providing a distraction to unwanted symptoms such as nausea, pain, anxiety, and insomnia. You can do this exercise alone, silently, or with a partner to read the exercise aloud.

Exercise: Guided Imagery- Script
Begin by getting into a comfortable seat/lying position. Close your eyes or bring your focus to something in the room/environment. Begin focusing on your breathing, each inhale and exhale entering and leaving your body. Notice the pattern of your breath- without feeling the need to change the pattern at all.

Start to Imagine being in a place that makes you feel calm…What do you notice around you? What do you see, hear, smell, feel, or even taste? Now imagine you have come to this place to do your favorite activity… What activity is this? How does it make you feel? Bring your attention back to your breath. Each inhale and exhale. What do you notice about its pattern?

Begin to bring physical awareness back into your body by wiggling your fingers and toes. Open your eyes slowly if they were closed. Notice how you feel, physically, mentally, emotionally after this brief exercise

Art Therapy:[70] Art therapy can help reduce perceptions of pain experiences. It differs from a distraction tool and instead helps patients modify and move their mental focus away from difficult emotions (e.g. stress, anxiety, etc.) that accompany pain to promote self-soothing and relaxation. Art Therapy involves working with a registered or board-certified art therapist to create an art piece, then explore how it relates to their pain and reflect on its implications.

Acupressure: Acupressure stems from traditional Chinese medicine and involves stimulating acupuncture points, but pressure is used instead of needles to relieve pain. Acupressure can be helpful in the care of patients who experience nociceptive or neuropathic pain, both in the acute and chronic setting.

Instructions and demonstrations for commonly used acupressure points

Nausea & Vomiting: https://www.mskcc.org/cancer-care/patient-education/acupressure-nausea-and-vomiting
Pain & Headaches: https://www.mskcc.org/cancer-care/patient-education/acupressure-pain-and-headaches
Stress & Anxiety: https://www.mskcc.org/cancer-care/patient-education/acupressure-stress-and-anxiety

Other acupressure resources include **weighted blankets, weighted vests, and SeaBands.**

Music Therapy: Music therapy offers diversion, distraction, and enhanced relaxation and may benefit patients experiencing pain. Alongside a specialty trained music therapist, patients engage in active music making, lyric writing, and song selection that is meaningful to them

Self-Hypnosis:[71] Self-hypnosis strengthens a patient's existing or under-developed skills in self-regulation capacities in order to shift attention or maintain focused attention to transform the experience of symptoms or illness experience. Clinicians who receive specialty training in self-hypnosis can successfully "coach" patients to access therapeutic self-suggestions and exercises.

Yoga: Yoga is a physical, mental, and spiritual (not religious) practice that calms the mind and body using different poses, exercises, breathing and meditation.

**Exercise: Easy Relax/Wind Down yoga sequence:*

			
Head Tilt/Rotations	***Seated Spinal Twist***	***Seated Cat/Cow***	***Forward Fold***
can be done sitting / standing	*seated on floor or chair*	*seated on floor or chair*	*on ground or bed with pillow props*
Beginning w/ left ear touching left shoulder, circle head towards chest in clockwise rotation w/ eyes open or closed a few times and then reverse and repeat counterclockwise	In a comfortable seat, bring left hand to right knee, right hand behind you. Inhale extend spine upwards, exhale, twist deeper. Repeat, twisting to left.	Place both hands on knees. Inhale, pull chest through bent arms, providing a slight back bend. Exhale, round back, extending arms, gazing at your belly. Repeat.	Extend legs in front of you (w/ slight bend in knees if more comfortable). Place pillows on top of legs. Fold upper body & arms over pillows and breathe.

****Helpful Applications & Additional Resources:*** There are many applications that offer additional resources and exercises related to mindfulness, meditation, yoga, self-hypnosis, breathing etc. These applications and more can be downloaded in the App Store.


Stop, Breathe, & Think


Headspace

Calm


Mind + Body

Consider **NCCIH.nih.gov** and MSKCC "**About Herbs App**"

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