Pediatric Pain and Symptom Management Guidelines

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Pain assessment in non-verbal children with neurological impairment (NI)

- Behaviors associated with pain in this population include: vocalizations (crying, moaning), facial expression (grimacing), consolability, interactivity (withdrawn), diminished sleep, movement (restless, increased movement of extremities), tone and posture (arching, stiffening), and physiological responses (diaphoresis, pallor, tachycardia)
- Core pain behaviors are consistently identified in this population yet each child will display a unique set of behaviors
- Unique behaviors can range from crying in one child to withdrawn in another and include idiosyncratic behaviors in some such as laughing, clapping, and blunted facial expression
- This unique and variable expression necessitates input from a consistent care provider, often a parent, with knowledge of a child's typical behavior patterns at baseline and in response to painful and non-painful (such as hunger) stimulus
- It is important to be vigilant to the possibility of pain in children with NI. There is often a focus on management of such problems as spasticity, autonomic dysfunction, or feeding intolerance without considering pain as a coexisting and exacerbating feature of these problems.
- Advantages of revised-FLACC: familiarity, ease of use, ability to individualize by adding behaviors specific to a child[1]
- Other tools available include the Paediatric Pain Profile[2] (PPP), available to download at www.ppprofile.org.uk following registration, and the Individualized Numeric Rating Scale[3] (INRS)

Revised-FLACC[1]				
Categories	0	1	2	Individualized behaviors*
Face	No particular expression or smile	Occasional grimace or frown; withdrawn or disinterested; appears sad or worried	Consistent grimace or frown; Frequent/constant quivering chin, clenched jaw; Distressed looking face; Expression of fright or panic; Other (write-in) _____	Examples: 'Pouty' lip; clenched and grinding teeth; eyebrows furrowed; stressed looking; stern face; eyes wide open, looks surprised; blank expression; non-expressive

Legs	Normal position or relaxed; usual tone and motion to limbs	Uneasy, restless, tense; occasional tremors	Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking Other (write-in) _____	Legs and arms drawn to center of body; clonus in left leg with pain; very tense and still; legs tremble
Activity	Lying quietly, normal position, moves easily; regular, rhythmic respirations	Squirming, shifting back and forth, tense or guarded movements; mildly agitated (e.g. head back and forth, aggression); shallow, splinting respirations, intermittent sighs	Arched, rigid or jerking; severe agitation; head banging; shivering (not rigors); breath holding, gasping or sharp intake of breaths, severe splinting Other (write-in) _____	Grabs at site of pain; nods head; clenches fists, draws up arms; arches neck; arms startle; turns side to side; head shaking; points to where it hurts; clenches fist to face, hits self, slapping; tense, guarded, posturing; thrashes arms; bites palm of hand; holds breath
Cry	No cry, no verbalization	Moans or whimpers; occasional complaint; occasional verbal outburst or grunt	Crying steadily, screams or sobs, frequent complaints; repeated outbursts, constant grunting Other (write-in) _____	States, 'I'm okay' or 'All done'; mouth wide open; states 'Owie' or 'No'; gasping, screaming; grunts or short responses; whining, whimpering, wailing, shouting; asks for medicine; crying is rare
Consolability	Content and relaxed	Reassured by occasional touching, hugging or being talked to; distractible	Difficult to console or comfort; pushing away caregiver, resisting care or comfort measures Other (write-in) _____	Responds to cuddling, holding, parent, stroking, kissing; distant and unresponsive when in pain

*Examples of additional pain behaviors identified by parents[1]

Guideines:

1. Review with parent or other caregivers to identify behaviors and features that appear to indicate pain
2. Indicate behaviors on the R-FLACC, adding those not listed
3. Use to indicate to others the child's pain behaviors and to document total pain score as needed

This booklet is a guide to symptom management in children and a tool for identifying areas for self-study. Pharmacologic options for pain and other distressing symptoms are provided. Non-pharmacologic interventions are an essential part of all symptom management.

Guidelines for Pharmacological Management of Pain

1. Pain management is guided by the World Health Organization (WHO) analgesic ladder
   a. Chose the drug based on degree of pain (mild, moderate, severe)
      Step 1 – Mild Pain
         Non-opioid ± adjuvant agent
      Step 2 – Mild to Moderate Pain OR Pain Uncontrolled after Step 1
         Opioid prn ± non-opioid around the clock (ATC) ± adjuvant agent
      Step 3 – Moderate to Severe Pain OR Pain Uncontrolled after Step 2
         Opioid ATC + PRN (converted to sustained release when dose established) ± non-opioid ± adjuvant agent
   b. When an analgesic in one category is not effective, utilize an analgesic from the next step of the ladder
   c. Choose the least invasive route – oral and sublingual (SL) preferred when possible
   d. Choose the dose and dose interval – for persistent, chronic pain (e.g. cancer pain), an opioid should be given scheduled around the clock, typically every 4 hours for oral or continuous for IV
   e. Once the daily opioid requirement is determined it can be converted to a sustained release given two or three times daily with immediate release used as needed for breakthrough pain
   f. Provide breakthrough (rescue) doses – typically 10-15% of the 24-hour opioid requirement, available as often as every 1-2 hour prn for oral
   g. Opioid titration – increase by 30-50% for moderate pain, 50-100% for severe pain
   h. If more than 3-4 doses of breakthrough medication are used daily for chronic pain, increase the dose of the sustained release opioid by an amount equivalent to 50-100% of the total amount of breakthrough medication used in 24 hours
   i. Manage side effects – initiate bowel regimen when starting an opioid
2. Consider using both non-opioids and opioids to maximize pain relief

3. Adjuvants enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and/or provide independent analgesic activity for specific types of pain. Examples include anti-depressants such as nortriptyline (neuropathic pain), anticonvulsants such as gabapentin and pregabalin (neuropathic pain), steroids (hepatic distention, bowel wall edema, cerebral edema), bisphosphonates (bone pain due to metastases), and radiation therapy (bone pain due to metastases).
4. Infants < 6 months of age require lower initial opioid dosing, approximately 25-50% of the opioid doses provided.
5. Use of combination products (e.g. acetaminophen with oxycodone) is NOT recommended. An increase in the dose can result in liver toxicity due to an increase in the acetaminophen dose.
6. Codeine is NOT recommended as up to 1/3 of children gain no analgesic effect due to inability to convert to the active metabolite morphine and can result in toxicity in others who are ultrarapid-metabolizers.
7. There is no “absolute” ceiling for opioids. Titrate to symptom control or intolerable side effects.
8. Consider opioid rotation (changing from one opioid to another) when side effects become intolerable.
9. Inadequate pain management more commonly requires dose escalation, not opioid rotation.
10. The safest opioids in renal impairment: fentanyl and methadone
11. Consider using Naloxone only if conservative measures, such as tactile stimulation, show no effect. See page 6 for dose.
12. Factors that can aggravate pain must be considered: poorly controlled pain, other symptoms (insomnia, nausea), psychosocial (depression, anxiety, family stress), cultural, spiritual
13. Non-pharmacologic interventions should be integrated into pain management (cuddling, massage, heat, cold, physical and occupational therapy, guided imagery, meditation, hypnosis, distraction, Reiki, story telling, music and art therapy)

Non-Opioids used for **Mild Pain** (maximum weight 50 kg)				
Medication		**Initial Dose (max)**	**Interval**	**Dosage forms**
Acetaminophen	PO PR	10 – 15 mg/kg (325 – 650 mg) Maximum 4 g/day	4-6 hrs	Many available doses
Ibuprofen	PO	6 – 10 mg/kg (400 – 600 mg)	6-8 hrs	40 mg/ml, 100 mg/5 ml; 200 mg
Naproxen*	PO	5 – 7 mg/kg (250 – 500 mg)	8-12 hrs	125 mg/5 ml; 220*, 250 mg
Ketorolac	IV	0.5 – 0.6 mg/kg (30 mg) Maximum 5 days	6-8 hrs	15 and 30 mg/ml for injection
Choline Magnesium Trisalicylate	PO	10 – 20 mg/kg (500-1000 mg)	8 hrs	500 mg/5 ml; 500, 1000 mg
Celecoxib	PO	22-50 kg 50 mg >50 kg 100 mg (100-200 mg)	12 hrs	100, 200 mg
Moderate Pain				
Tramadol**	PO	1 – 2 mg/kg (50 – 100 mg)	4-6 hrs	5 mg/1 ml; 50 mg; ER 100, 200, 300 mg

1. *Dosage indicated as Naproxen base; 200 mg Naproxen base is equal to 220 mg Naproxen sodium.
2. **Tramadol has a ceiling effect. If using >8 mg/kg/day (max 400 mg), change to an opioid for severe pain. DO NOT use with opioids. Caution: patients with seizures, on drugs that are inhibitors of cytochrome P450 2D6 isoenzyme (metoclopramide, TCAs) or drugs associated with serotonin syndrome (see table on page 21)

Opioid Conversion (reduce calculated equivalent dose by 25-50%)***

Drug	**Equianalgesic Dose**	
	Oral (mg)	IV (mg)
Morphine	30	10
Hydromorphone	6-8	1.5-2
Oxycodone	15-20	N/A
Fentanyl	N/A	0.1 (100 mcg)
Methadone	See methadone conversion table	

Opioids for **Severe Pain** in children > 6 months (maximum weight for dosing is 50 kg)			
Medication (dosage forms)	**Route**	**Initial Dose (initial maximum)**	**Interval**
Morphine 10 mg/5 ml, 20 mg/5 ml, 20 mg/1 ml; 10, 15, 30 mg; SR 15, 30, 60 mg	PO, SL	0.2-0.3 mg/kg (10 – 15 mg)	3-4 hr
	IV, SubQ	0.1 mg/kg (5 mg)	2-4 hr
Hydromorphone 1 mg/1 ml; 2, 4, 8 mg	PO, SL	0.04-0.06 mg/kg (2 mg)	3-4 hr
	IV, SubQ	0.015-0.02 mg/kg (0.75-1 mg)	2-4 hr
Fentanyl Transdermal patch 12.5, 25, 50, 75, 100 mcg/hr; Buccal tablet 100, 200, 400, 600, 800 mcg	IV, SubQ	0.5-1 mcg/kg (25 – 50 mcg)	30 min
		0.5-1 mcg/kg/hr (25 – 50 mcg/hr)	continuous
Methadone 5 mg/5 ml, 10 mg/5 ml, 10 mg/1 ml (be mindful of concentration used); 5, 10 mg	PO, SL	0.1 mg/kg (5 mg)	8-12 hr
	IV, SubQ	0.05-0.1 mg/kg (2.5 mg)	8-12 hr
Oxycodone 5 mg/5 ml, 20 mg/1 ml; 5, 15, 30 mg; SR 10, 20, 40, 60 mg	PO	0.1-0.2 mg/kg (5 – 10 mg)	3-4 hr

1. Fentanyl 25 mcg/hr patch approximately 50 mg/day oral morphine
2. Methadone requires expertise. PO to IV ratio is 2:1. Biphasic elimination may result in drug toxicity 3-7 days after starting or increasing methadone
3. ***Opioid conversion: reduce calculated dose of new opioid by 25-50% (25%-mild pain, 50%-no pain) due to incomplete cross-tolerance (e.g. differences in structure of opioids and affinity for various mμ receptors)

Opioid induced respiratory depression

Naloxone low dose for chronic opioid use: 1-2 mcg/kg (maximum 0.08 mg) IV at 2-3 minute intervals until response, half-life is less than most opioid agonists, be prepared for the need to re-administer naloxone boluses or use an infusion

Sample opioid conversion calculation: A patient is on sustained release (SR) oxycodone 10 mg po Q 8 hour and 5 mg po Q 3-4 hour break through pain. Pain is well controlled, averaging one rescue dose of oxycodone each day. The care plan requires conversion to intravenous. You plan to initiate a continuous IV infusion of morphine.

1. Total daily dose of scheduled SR oxycodone: 10 mg x 3 = 30 mg
   Total daily dose of short acting oxycodone: 5 mg x 1 = 5 mg
   30 mg + 5 mg = 35 mg oxycodone/day
2. Convert to daily morphine
   20 mg of oral oxycodone = 10 mg of IV morphine

   or

   $$\frac{\text{20 mg oral oxycodone}}{\text{10 mg IV morphine}} = \frac{\text{35 mg oxycodone}}{\textbf{X} \text{ mg IV morphine}}$$

   X = 17.5 IV morphine/day
3. Reduce the equianalgesic dose by 25-50% for cross-tolerance = 9-13 mg IV morphine/day; then convert to hourly rate of 0.5 mg IV morphine/hour (12 mg IV morphine/day)

Methadone conversion to other opioids[4]

Equianalgesic Conversion to Methadone			
Oral morphine equivalent	Mg of oral Methadone	= (ratio)	Mg of oral Morphine
<100 mg/day	1		3-4
100-300 mg/day	1		5-8
301-600 mg/day	1		10
601-800 mg/day	1		12
801-1000 mg/day	1		15
>1000 mg/day	1		20
IV methadone is twice as potent as oral methadone			

1. Due to incomplete cross-tolerance the initial calculated methadone dose should be reduced by 25-50% and then divided into 3 doses given Q 8 hrs
2. Consider baseline EKG based on risk of prolonged QTc, such as when combined with other medications, and goals of care
3. Potential drug interactions (partial list of drugs):
   a. Decrease effect of methadone (or increase effect when discontinued): phenobarbital, phenytoin, carbamazepine
   b. Increase effect of methadone: ciprofloxacin, erythromycin, diazepam, metronidazole, TCA, fluconazole
   c. Increase risk of QTc prolongation: TCA, neuroleptics, levofloxacin

Neuropathic pain and Neuro-irritability* (Maximum weight 50 kg)

Gabapentinoids

Thought to inhibit excitation by binding to the alpha-2-delta subunit of voltage dependent calcium ion channels in the CNS

Gabapentin (250 mg/5 ml; 100, 300, 400 mg)

Day 1-3 5 mg/kg/dose (250 mg maximum) PO qhs
Day 4-6 2.5 mg/kg/dose am and midday and 5 mg/kg qhs
Day 7-9 2.5 mg/kg/dose am and midday and 10 mg/kg qhs
Day 10-12 5 mg/kg/dose am and midday and 10 mg/kg qhs

Increase every 3-4 days by 5 mg/kg/day until[5]

1. Effective analgesia reached – to determine if effective, titrate to suggested minimum total dose of 40-60 mg/kg/day for children <5 years and 30 mg/kg/day for children >5 years of age
2. Side effects experienced (nystagmus, sedation, tremor, ataxia, swelling)
3. Maximum total dose of 50-75 mg/kg/day reached (2400-3600 mg/day)
4. Half of the total daily dose may be given as the evening dose if symptoms occur mostly in the evening and overnight
5. Titrate more rapidly for severe pain or as tolerated

Pregabalin (25, 50, 75, 100, 150, 200, 300 mg)

Day 1-3 1 mg/kg/dose (50 mg maximum) PO qhs
Day 4-6 1 mg/kg/dose PO q 12 hour

Increase every 3 days to 3 mg/kg/dose PO q 12 hour (maximum 6 mg/kg/dose)

Tricyclic Antidepressants (TCA)

Presynaptic reuptake inhibition in the CNS of norepinephrine and serotonin

Nortriptyline[5] (10 mg/5 ml; 10, 25, 50, 75 mg)

Day 1-4 0.2 mg/kg (maximum 10 mg) PO qhs
Day 5-8 0.4 mg/kg PO qhs

Increase every 5th day by 0.2 mg/kg/day until

1. Effective analgesia or dosing reaches 1 mg/kg/day (maximum 50 mg/day)
2. Obtain plasma level and ECG before further dose escalation

*Neuro-irritability refers to neurologically impaired children with persistent pain behaviors, irritability, and agitation. Reasons to use gabapentin and nortriptyline in these children[6]

1. No nociceptive pain source is identified or symptoms persist despite treating identified sources (such as gastroesophageal reflux, constipation, spasticity)
2. Symptoms suggest visceral hyperalgesia or central pain (pain associated with feedings, intestinal gas, flatus and bowel movements)
3. Onset of symptoms weeks to months following surgery
4. Painful peripheral neuropathy associated with underlying condition
5. Symptoms include persistent muscle spasms and dysautonomia

Other medications used for neuropathic pain:
Anticonvulsants: valproic acid, carbamazepine, phenytoin, lamotrigine **Serotonin norepinephrine reuptake inhibitors:** duloxatine, venlafaxine **Cannabinoids**: dronabinol (studied in central pain from multiple sclerosis)

Other adjuvants used for pain management		
Topical agents	Lidocaine patch	Apply to intact skin to most painful area, may leave in place for up to 12-hours in a 24-hour period, OK to cut
NMDA antagonists	Ketamine[7-9]	0.1 mg/kg/hr IV continuous
Alpha-2-adrenergic agonists	Clonidine	Day 1-3 0.002 mg/kg PO qhs Day 4-6 0.002 mg/kg q 12 hours Day 7-9 0.002 mg/kg q 8 hours In addition: • 0.002 mg/kg q 4 hour prn "autonomic storm" • Doses may be increased to 0.004 mg/kg • Titrate more rapidly if tolerated
Corticosteroids	Dexamethasone	• Used for: increased intracranial pressure (ICP), cerebral edema, spinal cord compression, bowel obstruction, bowel wall edema, hepatic distention • 1-2 mg/kg (maximum 50-100 mg) IV load then 0.1 mg/kg (max 4 mg) IV q 6 hrs • Higher maintenance doses for spinal cord compression associated with higher incidence of side effects without greater benefit[10]
	Prednisone	Bone pain 0.5-1 mg/kg (max 40 mg) PO q 12 h
Benzodiazepine	Clonazepam (possible pain adjuvant)	0.005-0.01 mg/kg PO q 8-12 h (initial maximum 0.25-0.5 mg)

Management of Opioid Side Effects

General Approach For All Side Effects
- **Monitoring over several days for improvement** of mild symptoms, such as sedation and nausea, without any changes in dosing
- **Management of the side effect** (see below)
- **Dose reduction** of the opioid (preferably ONLY if good pain control)
- **Opioid rotation** (switching to an alternate opioid)

Respiratory depression
- Breathing often less labored with pain control and significant opioid-induced respiratory depression is unlikely with appropriate dosing
- Risk factors: over-medication, opioid naïve patient, renal impairment, other causes of CNS depression including other medications, patients with mild pain or whose pain has been acutely relieved by a procedure

Sedation and hyper-somnolence that persists (tolerance typically develops)
- Withhold less necessary drugs that are CNS depressants
- Give methylphenidate for persistent fatigue

Constipation
- Laxatives are required with opioid use
- Start with a stimulant (senna) ± stool softener (docusate)
- Consider adding miralax or lactulose
- For refractory patients on multiple laxatives: Methylnaltrexone 0.15 mg/kg (max 8-12 mg) QOD SubQ[11]

Urinary retention
- Consider bethanechol (0.2 mg/kg, max 10 mg, PO q 8 hr), bladder cathing

Nausea and vomiting
- Usually improves after several days
- Antiemetic, either scheduled or PRN ($5HT_3$ or D_2 receptor antagonists)

Pruritis[12]
- Ondansetron 0.15 mg/kg PO/IV (4-8 mg) q 8 h prn
- Nalbuphine 0.01-0.02 mg/kg (1.5 mg) IV q 6 h prn itching
- Opioid antagonists: naloxone and naltrexone
- Antihistamines not effective (opioid induced itching not histamine mediated)

Myoclonus
- Clonazepam, Baclofen

Delirium
- Assess for coexisting factors (drugs: anticholinergics; metabolic alterations: infection, dehydration, renal, liver, electrolyte, brain metastases)
- Consider use of neuroleptics (haloperidol, risperidone)

Hyperalgesia
- Consider adjuvants for pain to allow potential opioid reduction

General approach to symptom management and medication use[13]

- Assess for presence of symptom causing distress
- Assess for severity utilizing parental input and assessment tools available
- Evaluate for potential causes of each symptom
- Treat identified causes when possible and if consistent with goals of care
- Utilize available symptom management interventions
- Review any prior use of sedating medications to guide initial dosage
- Assess for improvement using tools and parental reporting (quantitative data is beneficial but assessment tools are not available for many symptoms and it is helpful to not become overly dependant on numbers)
    - Have the features indicating the symptom improved? (examples: crying, facial grimacing, spasms, arching, stiffening associated with pain; retching flushing, sweating with autonomic dysfunction)
    - Has the severity of the symptom improved?
    - Has the frequency and duration of the symptom decreased?
    - How much improvement in the severity or decrease in the frequency and duration does the parent estimate: is your child 25% improved, 50% improved, greater than 50% improved?
- Follow-up process
    - Identify the timeline in which improvement is expected
        - Depends on onset of action and need to titrate medication:
            - hours-days opioid, sucralfate
            - 3-7 days proton pump inhibitor (PPI)
            - 1-2 weeks gabapentin, tricyclic antidepressant
        - Depends on frequency of symptom
            - Shorter trial for daily symptoms, longer for intermittent
            - If there is limited to no benefit in the time interval, determine if the drug will be discontinued before initiating other interventions
            - If a drug is discontinued, determine if the drug must be tapered down before stopping (drugs to taper off if prolonged use include: opioids, benzodiazepines, baclofen, gabapentin, TCA, clonidine, SSRI, SNRI)

Discontinuation of opioids, benzodiazepines, and other drugs (limited studies)

- In general, baclofen, clonidine, and gabapentin: taper over 1-2 weeks (decrease by 15-20% every 2-3 days); benzodiazepines, opioids, TCA, and SNRI: typically require longer tapering, often over 6-12 weeks
- Patients on a continuous opioid or benzodiazepine for 1–3 days duration, decrease original dose by 20% each day; 4–7 days (13%–20%); 8–14 days (8%–13%); 15–21 days (3-8%); > 21 days (3%)[14]
- Patients on a long term oral benzodiazepine may require a taper over 6-12 weeks, though in some a taper up to 6 months in duration may be needed[15]
- Most importantly: 1) monitor for withdrawal symptoms and adjust the wean schedule as needed 2) consider other sources of symptoms identified

Medications for Symptom Management (maximum weight 50 kg)

Medications	Usual Starting Dose (maximum initial dose)	Dosage forms
Neurological problems		
Spasticity/Muscle Spasms		
Diazepam	0.05-0.2 mg/kg PO/IV q 6 hr prn (2.5-10 mg) (Short term use recommended for spasticity[16] consider intermittent use for muscle spasms)	5 mg/5 ml, 5 mg/ml; 2, 5, 10 mg
Tizanidine	0.04-0.05 mg/kg PO qhs (2 mg), increase up to 0.05-0.1 mg/kg q 8 hr (not well studied in children)	2, 4 mg
Baclofen	2.5-5 mg PO tid, increase every 3 days by 5-15 mg/day to maximum of 40 mg/day	10 mg
Myoclonus		
Clonazepam	0.005-0.01 mg/kg PO q 8-12 h (0.25-0.5 mg)	compounded 0.1 mg/ml; 0.5, 1 mg; oral dissolving tablet 0.125, 0.25, 0.5 mg
Seizures – break through meds for seizure > 3-5 minutes or seizure cluster		
Lorazepam	0.1 mg/kg PO/SL/PR, may repeat in 15 minutes x 2 (max dose 4 mg)	2 mg/ml; 0.5, 1, 2 mg
Midazolam	0.2 mg/kg PO/intranasal (10 mg)	2 mg/ml
Diazepam rectal gel (Diastat)	2-5 years 0.5 mg/kg Q 15 minutes x 3 doses 6-11 yrs 0.3 mg/kg Q 15 minutes x 3 doses > 12 yrs 0.2 mg/kg Q 15 minutes x 3 doses	Round dose to 2.5, 5, 10, 15, or 20 mg/dose

PO = per oral, SL = sublingual, PR = per rectum, IV = intravenous, SubQ = subcutaneous

Dysautonomia (features: agitation, flushing, sweating, tachycardia, retching)		
Clonidine (central acting alpha-2 adrenergic receptor agonist, reducing sympathetic outflow)	Day 1-3 0.002 mg/kg PO qhs (0.1 mg) Day 4-6 0.002 mg/kg q 12 hours Day 7-9 0.002 mg/kg q 8 hours In addition: 1. 0.002 mg/kg q 4 hour prn "autonomic storm" 2. Doses may be increased to 0.004 mg/kg 3. Titrate more rapidly if tolerated	compounded 0.1 mg/ml; 0.1, 0.2 mg
Cyproheptadine	0.08 mg/kg PO q 8 hr (4 mg) If no benefit in 5 days, increase each dose by 0.04-0.08 mg/kg	2 mg/5 ml; 4 mg
Gabapentin	See Neuropathic pain section	See page 10
Morphine Sulfate	0.2-0.3 mg/kg PO/SL q 3-4 hr prn "autonomic storm"	See page 8
Diazepam	0.05-0.2 mg/kg PO/IV q 6 h prn "autonomic storm" (2.5-10 mg)	See page 14
Anxiety/Agitation/Delirium*		
Lorazepam	0.025-0.05 mg/kg PO/SL/IV/SQ q 6 h prn (1-2 mg)	2 mg/ml; 0.5, 1, 2 mg
Clonazapam	0.005-0.01 mg/kg PO q 8-12 h (0.25-0.5 mg)	see page 14
Haloperidol	0.01-0.02 mg/kg PO q 8 h prn (0.5-1 mg) For acute agitation: 0.025-0.05 mg/kg PO, may repeat 0.025 mg/kg in one hour prn	2 mg/ml; 0.5, 1, 2 mg
Risperidone	0.25-0.5 mg in the pm or divided	1 mg/1 ml; 0.25, 0.5, 1 mg

*Difficult to distinguish anxiety, agitation (unpleasant state of arousal), and delirium (fluctuating disturbance of consciousness with an acute onset over hours to days) in young children. Consider causes and conditions with similar features: pain, metabolic disturbances, medication reactions (see table page 21), progression of neurodegenerative conditions, depression, and impaired sleep. Children with neurological impairment have a number of conditions that result in similar features of agitation and pain behaviors (neuropathic pain, visceral hyperalgesia, dysautonomia, muscle spasms, dystonia, impaired sleep).

Insomnia*		
Melatonin	2-3 mg PO QHS (may increase to 9 mg)	2, 3 mg
Ramelteon (melatonin receptor agonist)	4-8 mg PO QHS	8 mg
Trazodone	0.75-1 mg/kg PO qhs (12.5-50 mg)	50, 100 mg
Clonidine	0.002 mg/kg PO qhs (0.1 mg), increase to 0.004 mg/kg PO qhs if needed	See page 15
Fatigue		
Methylphenidate	0.05-0.1 mg/kg q am and q noon (2.5-5 mg)	5 mg/5 ml; 5, 10 mg
Modafinil (Provigel)	> 6 years of age: 100 mg/day weeks 1-2 then 200 mg/day weeks 3-4	100, 200 mg
Depression		
SSRI – Citalopram	10-40 mg, divided	10 mg/5 ml; 10, 20 mg
SNRI – Duloxatine (Cymbalta)	20 mg PO, titrate up to 60 mg q day, maximum 60 mg BID	20, 30, 40 mg
Venlafaxine (Effexor)	12.5-37.5 mg PO q day for 1 week, then BID, then increase by 12.5-37.5 mg q week, maximum 225 mg/day	25, 37.5, 50 mg; extended release (XR) 37.5, 75, 150 mg
Tetracyclic antidepressant – Mirtazapine (Remeron)	15-45 mg PO q day	15, 30, 45 mg (available as dissolving tablet)

SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin-norepinephrine reuptake inhibitor; Tetracyclic antidepressant may also improve sleep, anxiety, nausea and vomiting (multiple receptor properties)

*Consider and treat causes of sleep disruption, such as pain, dyspnea, obstructive apnea, depression, and anxiety.

Gastrointestinal symptoms		
Constipation		
Polyethylene Glycol (osmotic)	0.7-1.5 gm/kg qd (8.5 – 17 g qd)	17 g/packet
Senna (stimulant)	2-6 yrs 2.5 – 3.75 ml q day 1/2 tablet q day >6-12 yrs 5 – 7.5 ml q day 1 tablet q day	8.8 mg/5 ml; 8.6 mg tablet
Lactulose (osmotic)	15-30 ml PO bid or 5-10 ml q 2 h until stool	10 g/15 ml
Docusate (softener)	0.5-1 mg/kg PO 1-4 times per day	50 mg/5 ml; 50, 100 mg
Bisacodyl (stimulant)	1 suppository PR every day as needed	10 mg supp
Sodium phosphate enema	1 PR every other day as needed	Fleet® enema for children
Bowel Obstruction		
Octreotide	0.001-0.002 mg/kg (1-2 mcg/kg) SubQ, IV q 8 h OR 0.003-0.006 mg/kg/day (3-6 mcg/kg/day) continuous	
Dexamethasone	0.1 mg/kg PO/IV q 6 hrs (maximum 16 mg/day)	
Pseudo-obstruction		
Neostigmine	Test dose 0.01-0.02 mg/kg/dose IV in ICU for monitoring (bradycardia, hypotension, increased airway secretions and bronchial reactivity), titrate up to 0.08 mg/kg/dose if needed (0.5 mg IV ≅ 15 mg PO)	Injection 0.5 mg/ml, 1 mg/ml; 15 mg tablet

Anorexia/Weight Loss		
Dronabinol	0.05-0.1 mg/kg PO q 12 h (2.5-5 mg) May increase if tolerated to maximum of 10 mg bid (may also help with nausea)	2.5, 5, 10 mg
Megestrol acetate	Use in children > 10 years, 100 mg PO bid, If no effect in 2 weeks, double dose to 200 mg bid	40 mg/ml; 20, 40 mg
Cyproheptadine	0.08 mg/kg PO Q 8 hr (4 mg) No benefit in 5 days, increase each dose by 0.04-0.08 mg/kg	2 mg/5 ml; 4 mg
Nausea/Vomiting/Retching (receptor blocking properties indicated)		
Ondansetron 5-HT_3	0.15 mg/kg PO/IV q 8 h prn (4-8 mg)	4 mg/5 ml; 4, 8 mg
Metoclopramide D_2 – prokinetic	Prokinetic: 0.1-0.2 mg/kg PO/IV q 6 h (5-10 mg)	5 mg/5 ml; 5, 10 mg
Haloperidol D_2	0.01-0.02 mg/kg PO q 8 h prn (0.5-1 mg)	2 mg/ml; 0.5, 1, 2 mg
Promethazine H_1, Ach, weak D_2	0.25-0.5 mg/kg PO/IV q 4-6 h prn (12.5-25 mg)	6.25 mg/5 ml; 12.5, 25 mg
Diphenhydramine H_1	1 mg/kg PO/IV q 6 h prn (25-50 mg)	12.5 mg/5 ml; 25, 50 mg
Scopolamine Ach	Adolescents: 1.5 mg by transdermal patch q 72 h	patch
Aprepitant NK_1	Adolescents: 125 mg PO 1 hour prior to chemo, then 80 mg q day on days 2 & 3	40, 80, 125 mg
Lorazepam anxiety	0.025-0.05 mg/kg PO/SL/IV/SQ q 6 h prn (1-2 mg)	2 mg/ml; 0.5, 1, 2 mg
Dexamethasone reduce edema	0.1 mg/kg PO/IV q 6 h (maximum 16 mg/day)	0.5 mg/5 ml, 1 mg/1 ml
Cyproheptadine $5HT_2$, H_1 & Ach	See above – may benefit neurologically impaired children with retching and feeding intolerance	See above

Sources of Nausea and Vomiting

Central Sites	Causes	Receptors/ Mechanisms	Therapeutic Agents
Vomiting Center (VC)	Final common pathway with numerous inputs	Histamine (H_1) Acetylcholine (Ach) Serotonin (5-HT_2)	Antihistamines (Diphenhydramine, Promethazine) Anticholinergics (Scopalamine, Hyoscyamine) 5HT_2 antagonists (Cyproheptadine?)
Chemoreceptor Trigger Zone (CTZ)	<u>Medications</u> (chemo, opioids, antibiotics, anticonvulsants) <u>Metabolic imbalance</u> (hyponatremia, hypercalcemia, uremia, ketoacidosis) <u>Toxins</u> (ischemic bowel)	Serotonin (5-HT_3) Dopamine (D_2) Neurokinin (NK_1)	Serotonin antagonists (Ondansetron, Granisetron) Butyrophenones (Haloperidol, Droperidol) Phenothiazines (Prochlorperazine, Chlorpromazine) NK_1 antagonists (Aprepitant)
Vestibular	Disorders of the vestibular nucleus and cranial nerve VIII	Histamine (H_1) Acetylcholine (Ach)	Antihistamines (Diphenhydramine, Promethazine) Anticholinergics (Scopalamine, Hyoscyamine)
Meningeal Mechanoreceptors	Increased intracranial pressure, tumor, infection	Stimulation of the VC	Corticosteroids
Cortex	Anxiety	Stimulation of CTZ and VC	Relaxation Techniques Benzodiazepines, Dronabinol

Gastrointestinal Sites	Causes	Receptors/ Mechanisms	Therapeutic Agents
Mechanoreceptors and Chemoreceptors	Stasis (anticholinergics, opioids), constipation, autonomic neuropathy, mucositis, gastritis, radiation, chemo, tumor, hepatic distention	Vagal afferents (CN X)	H2-Blockers, PPI (Ranitidine, Omeprazole); Prokinetic Agents (Metoclopramide)
		Histamine (H1)	Antihistamines (Diphenhydramine, Promethazine)
		Serotonin (5-HT3)	Serotonin antagonists (Ondansetron, Granisetron)

Abbreviations: 5HT=serotonin, H=histamine, Ach=acetylcholine, D2=dopamine, NK=neurokinin, PPI=proton pump inhibitor

Respiratory Symptoms		
Dyspnea		
Morphine (or opioid equivalent)	0.1 mg/kg PO or 0.05 mg/kg IV/SQ q 3-4 h prn (5 mg PO, 2.5 mg IV) (or other opioids at equivalent dose)	10 mg/5 ml, 20 mg/ml
Lorazepam	0.025-0.05 mg/kg PO/SL/IV/SQ q 6 h prn (max dose 2 mg)	2 mg/ml
Midazolam	0.1-0.2 mg/kg PO/SL (5 mg)	2 mg/ml
Respiratory Secretions (use cautiously for chronic secretion management)		
Ipratropium	250-500 mcg nebulization Q 4-6 h prn	neb
Glycopyrrolate	0.04-0.05 mg/kg PO q 4-8 h (1-2 mg)	1, 2 mg
Atropine	1-2 drops SL q 4-6 h prn	0.5% ophthalmic drops
Scopalomine	Adolescents: 1.5 mg transdermal patch q 72 h	patch
Hyoscyamine	<u>0.125 mg/1 ml solution</u> 3-4 kg 4 drops PO q 4 hours prn 10 kg 8 drops PO q 4 hours prn 50 kg 1 ml (0.125 mg) PO q 4 hours prn	0.125 mg/1 ml
	<u>0.125 mg/5 ml elixir</u> 10 kg 1.25 ml PO q 4 hours prn 20 kg 2.5 ml PO q 4 hours prn 40 kg 3.75 ml PO q 4 hours prn 50 kg 5 ml (0.125 mg) PO q 4 hours prn	0.125 mg/5 ml

Chronic, persistent symptoms: consider pain and/or palliative care consult for assistance with symptom management; including care plans in the home or end-of-life symptom control

Escalating symptoms at end-of-life (pain, dyspnea, agitation) – DNR/DNI in place with goal of comfort

Consider Pain or Palliative Care Consult (check hospital policy)

Opioid escalation[17]

- Bedside titration with IV bolus every 10-15 minutes until pain is relieved
- If on opioids, initial bolus will be 10-20% of the 24 hour opioid dose
- Increase opioid bolus by 30-50% every third dose if pain continues
- Once patient has obtained adequate symptom relief, calculate the new 24 hour opioid dose including rescue doses
- Determine route for around the clock dosing that is best suited to patient's ongoing analgesic needs (oral, IV, transdermal)
- Consider adding an adjuvant or coanalgesic (eg, a nonsteroidal anti-inflammatory drug, benzodiazepine, corticosteroids, ketamine)
- If the patient has significant opioid adverse effects with adequate pain control, reduce the equianalgesic dose of the new opioid by 25-50%
- If the patient has significant opioid adverse effects without adequate pain control, rotate opioid without a reduction in the equianalgesic dose

Adjuvants

Lorazepam	0.05-0.1 mg/kg SL/IV q 4 hour
Midazolam	Loading dose 0.03-0.04 mg/kg (maximum 2 mg) then 0.03-0.06 mg/kg/hr IV/SubQ infusion titrated to effect • Loading dose may be repeated every 5 minutes until desired effect is achieved • Hourly maintenance dose 25-33% of the cumulative loading dose IV • For escalating symptoms, a bolus dose, equal to the hourly rate, may be given every 5-15 minutes IV prn discomfort • If > 3 bolus doses within an hour, the rate of the continuous infusion should be increased by 30%
Haloperidol	0.01-0.02 mg/kg PO q 8 h prn (0.5-1 mg) For acute agitation: 0.025-0.05 mg/kg PO, may repeat 0.025 mg/kg in one hour prn
Ketamine	0.1 mg/kg/hr IV continuous

Consult pain or palliative care teams for assistance and if symptoms remain intractable

Medication toxicities

The most common medication categories to consider include: antidopaminergic (neuroleptics) and SSRIs, paradoxical reactions possible from anticholinergics, benzodiazepines, and antihistamines

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, trazadone, 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 as examples)
Akathisia (unpleasant state of motor restlessness)	restlessness, distress, tension and discomfort	dopamine antagonists, TCAs, SSRIs, withdrawal from opioids, paradoxical reactions
Agitation (unpleasant state of arousal)	increased motor activity, autonomic arousal (diaphoresis, tachycardia), inability to relax	paradoxical reactions to many medications including anticholinergics, benzodiazepines, antihistamines, TCAs
Delirium	altered sleep-wake cycle, perceptual and psychomotor disturbances	anticholinergics, benzodiazepines, antihistamines, TCAs

Multiple sources used for this guide including: *Lexi Comp's Pediatric Dosage Handbook:* 16th ed; Schechter NL, Berde CB, Yaster M (Eds). Pain in Infants, Children, and Adolescents, 2nd Ed. Philadelphia: Lippincott Williams and Wilkins, 2003; http://www.hospicecare.com/manual/pain.html

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