Pediatric Pain and Symptom Management Guidelines

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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. Use of medications requires adequate knowledge of side effects and drug-drug interactions. These suggestions cannot replace medical judgment in how the individual characteristics of a patient influence decisions about the use of medications, including dosage. Many of these medications involve off-label use. Non-pharmacologic interventions are always an essential part of symptom management.

Guidelines for Pharmacological Management of Pain

1. Infants < 6 months of age require lower initial opioid dosing, approximately 25-50% of the opioid doses provided
2. Utilize your institutions developmentally appropriate symptom assessment tools to determine presence and severity of pain
3. The World Health Organization (WHO) recommends analgesic treatment in two steps according to the child's level of pain severity[1]
    a. Chose the drug based on degree of pain (mild, moderate or severe)
    Step 1 – Mild Pain
        Non-opioid ± adjuvant agent
    Step 2 – Moderate to Severe Pain OR Pain Uncontrolled after Step 1
        Opioid ± non-opioid ± adjuvant agent
    b. Choose the least invasive route – oral and sublingual (SL) preferred when possible
    c. 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
    d. 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
    e. Provide breakthrough (rescue) doses – typically 10-15% of the 24-hour opioid requirement, available as often as every 1-2 hour prn for oral
    f. Opioid titration – increase by 30-50% for moderate pain, 50-100% for severe pain
    g. 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
    h. Manage side effects – initiate bowel regimen when starting an opioid

4. Consider using both non-opioids and opioids to maximize pain relief
5. 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 amitriptyline and 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).
6. 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.
7. 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.
8. There is no “absolute” ceiling for opioids. Titrate to symptom control or to intolerable side effects.
9. Consider opioid rotation (changing from one opioid to another) when side effects become intolerable.
10. Inadequate pain management more commonly requires dose escalation, not opioid rotation.
11. The safest opioids in renal impairment: fentanyl and methadone
12. Consider using Naloxone only if conservative measures, such as tactile stimulation, show no effect. See page 6 for dose.
13. Factors that can aggravate pain must be considered: poorly controlled pain, other symptoms (insomnia, nausea), psychosocial (depression, anxiety, family stress), cultural, spiritual
14. Non-pharmacologic interventions should be integrated into pain management (cuddling, massage, heat, cold, warm baths, physical and occupational therapy, guided imagery, meditation, hypnosis, distraction, Reiki, story telling, music and art therapy, aromatherapy, weighted blankets and vibratory stimulation in children with neurological impairment)

Abbreviations:

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

SSRI=Selective serotonin reuptake inhibitor; SNRI=Serotonin-norepinephrine reuptake inhibitor, 5HT=serotonin, Ach=acetylcholine, D2=dopamine, H=histamine, ICP=increased intracranial pressure, NK=neurokinin, PPI=proton pump inhibitor, TCA=Tricyclic antidepressant

CBC, complete blood count; CMP, comprehensive metabolic panel (includes alkaline phosphatase; alanine aminotransferase; total bilirubin); UA, urine analysis; UCx, urine culture

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) Max 3 gm/day	4-6 hrs	Many oral dosage forms 160 mg/5ml liquid Supp 120 mg, 325 mg, 650 mg
	IV	12.5 mg/kg 15 mg/kg (650 mg) Max 75 mg/kg/day	4 hrs 6 hrs	10 mg/1 ml
Ibuprofen	PO	6 – 10 mg/kg (400 – 600 mg)	6-8 hrs	40 mg/ml, 100 mg/5 ml; 100, 200, 400, 600 mg
Naproxen*	PO	5 – 7 mg/kg (250 – 400 mg)	12 hrs	125 mg/5 ml; 220*, 250 mg
Ketorolac	IV	0.3 – 0.5 mg/kg (15-30 mg) Use up to 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
Celecoxib	PO	1 – 2 mg/kg (100 mg)	12-24 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 total daily), change to an opioid for severe pain. Use with opioids controversial. Caution: patients with seizures, on drugs that are inhibitors of cytochrome P450 2D6 isoenzyme or drugs associated with serotonin syndrome (see table on page 25)

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)

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, Subcut	0.05-0.1 mg/kg (2.5-5 mg)	2-4 hr
		20 mCg/kg/hr (1 mg) and 20 mCg/kg/hr PCA bolus (4-6/hr) lockout interval 5-10 min	continuous
Hydromorphone 1 mg/1 ml; 2, 4, 8 mg	PO, SL	0.04-0.06 mg/kg (1-2 mg)	3-4 hr
	IV, Subcut	0.015 mg/kg (0.2-0.6 mg)	2-4 hr
Fentanyl Transdermal patch 12, 25, 50, 75, 100 mCg/hr; Transmucosal options see page 24	IV, Subcut	0.5-2 mCg/kg (25-75 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; 5, 10 mg	PO, SL	0.1 mg/kg (5 mg)	4 hr first 2-3 doses, then 8-12 hr
	IV, Subcut	0.05-0.1 mg/kg (2.5-5 mg)	4 hr first 2-3 doses, then 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)	4-6 hr

1. **Fentanyl** 25 mCg/hr patch approximately 50 mg/day oral morphine (see page 24)
2. **Methadone** requires expertise. PO to IV ratio is 2:1. Biphasic elimination may result in drug toxicity 2-5 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 depressed respiratory rate

Naloxone low dose: dilute 0.4mg (1 ml) of naloxone in 9 ml of saline to yield 0.04 mg per ml, give 1-5 mCg/kg (maximum 0.04-0.2 mg) IV at 2-3 minute intervals until response, titrate to effect, half-life is less than most opioid agonists, be prepared for the need to re-administer naloxone boluses or use an infusion (0.5-2 mCg/kg/hour)

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 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)

Opioid conversion to methadone[2] (requires expertise)

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, rifampin, St John's wort
   b. Increase effect of methadone: ciprofloxacin, erythromycin, fluconazole, diazepam, SSRIs, venlafaxine, verapamil, aprepitant, sodium bicarbonate, grapefruit
   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[3] (250 mg/5 ml; 100, 300, 400 mg)

Day 1-3 2 mg/kg (100 mg) PO TID **OR** 5 mg/kg/dose (250 mg max) PO qhs
Day 4-6 4 mg/kg TID **OR** 2.5 mg/kg/dose am and midday and 5 mg/kg qhs
Day 7-9 6 mg/kg TID **OR** 2.5 mg/kg/dose am and midday and 10 mg/kg qhs
Day 10-12 8 mg/kg TID **OR** 5 mg/kg/dose am and midday and 10 mg/kg qhs

Increase every 2-4 days by 5-6 mg/kg/day until

1. Effective analgesia reached (often noted at 30-45 mg/kg/day)
2. Side effects experienced (nystagmus, sedation, tremor, ataxia, swelling)
3. Maximum total dose of 50-72 mg/kg/day reached (2400-3600 mg/day)
4. Younger children (<5 years) may require a 30% higher mg/kg/day dosing, such as a total dose of 40-60 mg/kg/day[4, 5]
5. Half of the total daily dose may be given as the evening dose if symptoms occur mostly in the evening and overnight
6. Titrate more rapidly for severe pain or as tolerated

Pregabalin (20 mg/1 ml; 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 2-4 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

Amitriptyline (10, 25, 50, 75 mg) **or Nortriptyline**[3] (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 4-5 days 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; higher rate of side effects with higher doses including anti-cholinergic; consider twice daily dosing of 25-30% in the am and 70-75% in the evening

*Neuro-irritability: refers to neurologically impaired children with persistent pain behaviors, irritability, and agitation. See page 21 for suggested neuro-pain ladder and page 22 for further suggestions.

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

Other adjuvants used for pain management		
Topical agents	Lidocaine patch	Apply to intact skin over most painful area, may leave in place for up to 12-hours in a 24-hour period, OK to cut
NMDA antagonists	Ketamine[6-8]	0.05-0.1 mg/kg/hr IV continuous 0.25-0.5 mg/kg PO q 6-8 hours
Alpha-2-adrenergic agonists	Dexmedetomidine	0.2-1 mCg/kg/hr IV
	Clonidine	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: • Doses may be increased by 0.002 mg/kg as tolerated (monitor for hypotension), average dose for spasticity in one study 0.02 mg/kg/day (range 0.0014-0.15 mg/kg/day) • Titrate more rapidly as 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[9]
	Prednisone	Bone pain 0.5-1 mg/kg (max 40 mg) PO q 12 h
Benzodiazepine	Clonazepam	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 constipation on multiple laxatives: Naloxone 0.25-2 mCg/kg/hr[10, 11] Methylnaltrexone 0.15 mg/kg (max 8-12 mg) q 48 hours subcut[12]

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[13]

- 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 (0.25-2 mCg/kg/hour, titrate to effect), 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 a neuroleptic (haloperidol, risperidone, olanzapine, see page 13)

Hyperalgesia

- Consider adjuvants (page 9) for pain to allow potential opioid reduction

General approach to symptom management and medication use[14]

- Assess for presence of symptom causing discomfort and distress
- Assess the severity as well as the frequency and duration of episodes
- Evaluate for causes and treat when possible (and if consistent with goals of care)
- Utilize available symptom management interventions, including non-pharmacologic
- Review current medications so as to minimize drug-drug interactions (see page 25) and minimize using several drugs with the same mechanism of action (increases risk of side effects from that mechanism of action)
- Determine initial dose, factoring in prior response to sedating medications and the priority of goals (minimize sedation or maximize symptom improvement)
- Determine minimum dose for drugs that require titration to ensure an adequate trial
- Identify the timeline in which improvement is expected
  - Depends on onset of action and need to titrate medication over time
    - hours-days opioid, sucralfate
    - 3-7 days proton pump inhibitor (PPI)
    - 1-3 weeks gabapentin, tricyclic antidepressant, clonidine
  - Depends on frequency of symptoms
    - Shorter trial for daily symptoms, longer for intermittent
- Assess for improvement using tools (when available) and parental reporting
  - Have the features indicating the symptom improved? (examples: moaning, facial grimacing, spasms, arching, stiffening indicating pain in a nonverbal child with impairment of the CNS; retching, flushing, sweating with autonomic dysfunction)
  - Has the severity of the symptom improved?
  - Has the frequency and duration of distressing events decreased?
  - How much improvement does the parent estimate: is your child 25% improved, 50% improved, greater than 50% improved?
- If there is limited to no benefit in the time interval, determine if the drug will be discontinued before initiating other interventions; some drug combinations with different mechanisms of action may have benefit when there is partial benefit from the initial drug, such as the combination of gabapentin and nortriptyline[15]
- If a drug is discontinued, drugs to taper off after prolonged use include: opioids, benzodiazepines, baclofen, gabapentin, TCA, clonidine, SSRI, SNRI

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

- **General guidelines**: baclofen, clonidine, and gabapentin, taper off over 2-4 weeks (decrease by 10-20% of the original dose every 2-3 days); benzodiazepines, opioids, TCA, and SNRI, typically require longer tapering, often over 4-12 weeks
- Patients on a long term oral benzodiazepine require a slow taper over 6-12 weeks, such as a decrease by an amount that is 10% of the original dose every 7 days, though in some a taper up to 6 months in duration may be needed[16]
- Study of patients in hospital on continuous opioid or benzodiazepine: guidelines for 1–3 days duration, decrease original dose by 20% each day; 4–7 days, decrease by 13%–20% daily; 8–14 days (8%–13%); 15–21 days (3-8%); > 21 days (3%)[17]
- In general: 1) monitor for withdrawal symptoms and adjust the wean schedule as needed, 2) consider other sources if symptoms identified during taper, 3) potential for more harm from tapering too quickly than from tapering too slowly

Medications for Symptom Management (maximum weight 50 kg)

Medication	Usual Starting Dose (maximum initial dose)	Dosage forms
Neurological problems		
Spasticity/Muscle Spasms		
Baclofen	2.5-5 mg PO q 8 hr, increase every 3 days by 5-15 mg/day to maximum of 60-80 mg/day; average dose in study: 1.9 mg/kg/day (range 0.14-9.9 mg/kg/day)[18]	compounded 10 mg/1 ml; 10, 20 mg
Clonidine	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. Titrate more rapidly if tolerated 2. Average dose in study: 0.02 mg/kg/day[18]	compounded 0.1 mg/ml; 0.1, 0.2 mg; 0.1, 0.2, 0.3 mg/day transdermal patch (see page 24)
Tizanidine	0.04-0.08 mg/kg PO qhs (2-4 mg), increase up to 0.16 mg/kg q 8 hr (max 8-12 mg q 8 hr) (Not well studied in children)	2, 4 mg
Diazepam	0.03-0.05 mg/kg PO/IV q 6-8 hr (2 mg), titrate to effect, maximum dose 10 mg (Short term use recommended for spasticity[19] consider intermittent use for muscle spasms)	5 mg/5 ml, 5 mg/ml; 2, 5, 10 mg
Myoclonus		
Clonazepam	0.005-0.01 mg/kg PO q 8-12 hr (0.25-0.5 mg) Increase every 3 days up to 0.05-0.1 mg/kg PO q 8-12 hr (max 0.2 mg/kg/day)	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/buccal/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 buccal/intranasal (10 mg)	2 mg/ml buccal 5mg/ml IV soln
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, 7.5, 10, 12.5, 15, 17.5 or 20 mg/dose
Anti-epileptic drugs (AEDs) that can be given rectally, if needed: carbamazepine, phenobarbital, lamotrigine, and valproic acid (see page 24)		

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. 0.002-0.004 mg/kg q 4 hour prn "autonomic storm" 2. Average dose for spasticity in one study: 0.02 mg/kg/day (0.0014-0.15 mg/kg/day)[18] 3. Titrate more rapidly if tolerated	compounded 0.1 mg/ml; 0.1, 0.2 mg; 0.1, 0.2, 0.3 mg/day transdermal patch (see page 24)
Gabapentin	See Neuropathic pain section	See page 8
Morphine Sulfate	0.2-0.3 mg/kg PO/SL q 3-4 hr prn "autonomic storm"	See page 6
Cyproheptadine (for associated retching)	0.08 mg/kg PO q 8 hour (4 mg) If no benefit in 5 days, increase each dose by 0.04-0.08 mg/kg, up to 0.16 mg/kg TID	2 mg/5 ml; 4 mg
Propranolol	0.2-0.4 mg/kg PO q 8 hr (20 mg), increase every 3 days up to 1.6 mg/kg q 8 hr (80 mg)	20 & 40 mg/5 ml; 10, 20, 40, 60 mg
Anxiety/Agitation/Delirium*		
Lorazepam	0.02-0.05 mg/kg PO/SL/IV/subcut q 6 h prn (1-2 mg)	2 mg/ml; 0.5, 1, 2 mg
Clonazapam	See myoclonus, page 12	See page 12
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 PO in the pm or divided, titrate every 1-2 days, maximum 3 mg total/day	1 mg/1 ml; 0.25, 0.5, and 1 mg
Olanzapine	1.25-2.5 PO daily, increase weekly if needed, up to 5 mg daily	2.5, 5, 7.5, 10, 15, 20 mg (ODT not available in 2.5 or 7.5)
Quetiapine	25 mg BID, increase daily by 25 mg/dose, maximum 100-200 mg BID	25, 50, 100, 200 mg; ER 50, 150 mg

*__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 21-22 for symptom treatment guidelines and suggestions in children with NI.

Insomnia*		
Melatonin	2-3 mg PO qhs, may increase to 12 mg	2, 3, 5 mg
Ramelteon (melatonin receptor agonist)	4-8 mg PO qhs	8 mg
Trazodone	0.75-1 mg/kg PO qhs (25-50 mg), increase every 1-2 weeks up to 150 mg	50, 100, 150 mg
Clonidine	0.002 mg/kg PO qhs (0.1 mg), increase by 0.002 mg/kg PO qhs if needed, maximum 0.008 mg/kg qhs (0.4 mg)	See page 12
Fatigue		
Methylphenidate	0.05-0.1 mg/kg q am and q noon (2.5-5 mg)	5 mg/5 ml, 10 mg/5 ml; 5, 10 mg
Modafinil (Provigil)	> 6 years of age: 100 mg/day weeks 1-2 then 200 mg/day weeks 3-4	100, 200 mg
Depression		
SSRI – Citalopram	5-10 mg PO q day, increase every 2 weeks up to maximum of 40 mg q day	10 mg/5 ml; 10, 20 mg
Sertraline	12.5-25 mg q day, increase weekly up to 100-200 mg daily	20 mg/ml; 25, 50, 100 mg
SNRI – Duloxetine (Cymbalta)	20-40 mg PO q day, increase weekly up to 60 mg q day, maximum 60 mg BID	20, 30, 60 mg (do not crush, capsules are extended release)
Tetracyclic antidepressant – Mirtazapine (Remeron)	15 mg PO q day, increase weekly up to 45 mg 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 (see also management of opioid side effects page 10)		
Polyethylene Glycol (osmotic)	0.7-1.5 gm/kg qd (8.5 – 17 g qd)	17 gm/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 10 mg supp (also available in combination with docusate)
Docusate (softener)	0.5-1 mg/kg PO 1-4 times per day	50 mg/5 ml; 50, 100 mg
Lactulose (osmotic)	15-30 ml PO bid or 5-10 ml q 2 h until stool	10 gm/15 ml
Milk of Magnesia (osmotic)	15-30 ml PO daily or bid, give scheduled or as needed	Liquid
Bisacodyl (stimulant)	1 suppository PR every day as needed	5 mg tablet 10 mg supp
Sodium phosphate enema	1 PR every other day as needed	Fleet® enema for children
Intestinal Motility		
Erythromycin	2-5 mg/kg PO 4 times daily (maximum 250 mg per dose)	200 mg/5 ml
Bowel Obstruction		
Octreotide	0.001-0.002 mg/kg (1-2 mCg/kg) Subcut, IV q 8 h OR 0.003-0.006 mg/kg/day (3-6 mCg/kg/day) continuous	
Acute Colonic Pseudo-obstruction		
Neostigmine[20-22]	IV 0.01-0.02 mg/kg (max 0.5-1 mg) with monitoring (risk for bradycardia, hypotension, increased airway secretions and bronchial reactivity), titrate up to 0.08 mg/kg/dose if needed[20, 21] OR Subcut 0.5 mg (0.25 to 1.25 mg)[22]	Injection 0.5 mg/ml, 1 mg/ml; 15 mg tablet (0.5 mg IV ≅ 15 mg PO)

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	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 (max 400 mg bid)	40 mg/ml; 20, 40 mg
Cyproheptadine	0.08 mg/kg PO TID (4 mg) If 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
Olanzapine D_2, $5HT_2$, $5HT_3$, H_1	See Anxiety/Agitation/Delirium on page 13	See page 13
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	0.02-0.05 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
Dronabinol	See above	See above
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 ($5\text{-}HT_2$)	Antihistamines (Diphenhydramine) Anticholinergics (Scopalamine) $5HT_2$ antagonists (Cyproheptadine)
Chemoreceptor Trigger Zone (CTZ)	Medications (chemo, opioids, antibiotics, anticonvulsants) Metabolic (hyponatremia, hypercalcemia, acidosis, uremia) Toxins (ischemic bowel)	Serotonin ($5\text{-}HT_3$) Dopamine (D_2) Neurokinin (NK_1)	Serotonin antagonists (Ondansetron, Granisetron) Butyrophenones (Haloperidol, Droperidol) Atypical antipsychotic (Olanzapine) NK_1 antagonists (Aprepitant)
Vestibular	Disorders of the vestibular nucleus and cranial nerve VIII	Histamine (H_1) Acetylcholine (Ach)	Antihistamines (Diphenhydramine) Anticholinergics (Scopalamine)
Meningeal Mechanoreceptors	Increased ICP, tumor, infection	Stimulation of the VC	Corticosteroids
Cortex	Anxiety	Stimulation of CTZ and VC	Relaxation Techniques, Benzodiazepine, Dronabinol
Gastrointestinal Sites			
Mechanoreceptors and Chemoreceptors	Drugs, (opioids, anticholinergics), constipation, autonomic neuropathy, mucositis, gastritis, chemo, radiation, tumor, hepatic distention	Vagal afferents (CN X) Histamine (H1) Serotonin (5-HT3)	H2-Blockers, PPI (Ranitidine, Omeprazole); Prokinetic Agents (Metoclopramide) Antihistamines (Diphenhydramine) Serotonin antagonists (Ondansetron, Granisetron)

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

Respiratory Symptoms		
Dyspnea		
Morphine (or opioid equivalent)	0.05-0.1 mg/kg PO or 0.015-0.03 mg/kg IV/subcut 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	0.02-0.05 mg/kg PO/SL/IV/subcut q 6 h prn (max dose 2 mg)	2 mg/ml
Midazolam	0.1-0.2 mg/kg PO/SL (5-10 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) 0.004-0.005 mg/kg (4-10 mCg/kg) IV q 3-4 h	0.2 mg/1 ml; 1, 2 mg
Atropine	1-2 drops SL q 4-6 h prn	1% 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

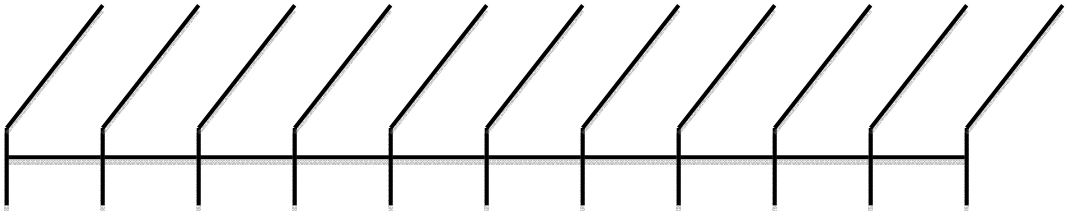
Pain assessment in non-verbal children with neurological impairment (NI)[24]

- Behaviors associated with pain in this population include (examples noted with Revised-FLACC): 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 source of these problems (see pages 21-22)
- Advantages of revised-FLACC[25] and Individualized Numeric Rating Scale (INRS)[26]: ease of use and ability to individualize by adding behaviors specific to a child
- Other tools available include the Paediatric Pain Profile[27] (PPP), available to download at www.ppprofile.org.uk following registration
- See examples of pain behaviors in revised-FLACC

Revised-FLACC[25]				
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

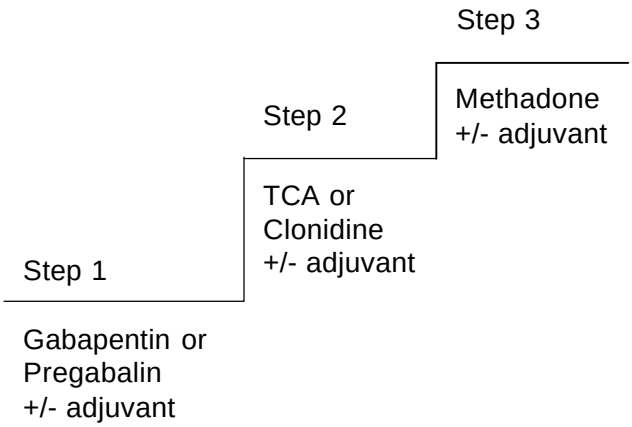
Activity	Lying quietly, normal position, moves easily; regular, rhythmic respirations	Squirming, shifting back and forth, tense or guarded movements; mildly agitated (e.g. head back and forth); splinting respirations, intermittent sighs	Arched, rigid or jerking; severe agitation; head banging; shivering (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, shouting; 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[25] Guideines: 1. Review with parent/caregivers to identify behaviors and features that can 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 pain score as needed				

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)[26]



0 5 10

Proposed neuro-pain ladder for children with severe neurological impairment[28, 29]



- **Neuro-pain**: used to indicate children with SNI and persistent pain behaviors despite treatment of a potential nociceptive source or when no source is identified
- **Evaluate for nociceptive sources** (if not already done)**:**
  - Blood tests (CMP, CBC, amylase, lipase); urine (UA/UCx); gastric pH and guaiac (from G-tube); X-ray or bone scan if fracture suspected; dental exam if no recent exam; renal ultrasound if on topiramate or ketogenic diet (risk of renal stones)
  - **Do not delay empiric symptom treatment**: in child with history of intermittent agitation/irritability/discomfort and negative tests, initiate gabapentin trial while considering further studies, given its safety and potential for benefit
  - Other tests (such as abdominal and renal ultrasound, or endoscopy) as indicated by initial evaluation or in children with no history of intermittent irritability
- **Reasons to initiate an empiric trial with gabapentin or pregabalin**[29] (gabapentin used as young as 1-month in term infants with an insult to the CNS, such as HIE)
  - No nociceptive pain source is identified following initial evaluation
  - History of intermittent agitation/irritability/discomfort that has increased over time
  - Symptoms persist despite treating identified or potential sources (such as GERD)
  - Symptoms suggest central neuropathic pain or visceral hyperalgesia (symptoms associated with feedings, intestinal gas, flatus and bowel movements)
  - Symptoms include sudden bursts of intense, recurrent pain behaviors
  - Onset of symptoms noted weeks to months following surgery
  - Painful peripheral neuropathy associated with underlying condition
  - Symptoms include persistent muscle spasms or dysautonomia
- **Non-pharmacologic interventions** include vibrating mats and weighted blankets
- **Steps 2 and 3**: pain that is unrelieved by a medication in the previous step
  - TCA (amitriptyline, nortriptyline) for continued pain with associated GI symptoms
  - Clonidine for continued autonomic dysfunction and muscle spasms
  - Some may prefer to use methadone in step 2, though requires expertise in use
- **Adjuvant**: medications used to enhance the benefit of other treatment:
  - Break through pain: prn acetaminophen, ibuprofen, tramadol or opioid
  - Autonomic storms: prn clonidine, opioid, or benzodiazepine
  - Spasms/spasticity: prn clonidine or benzo; scheduled baclofen or clonidine
  - Retching/vomiting: cyproheptadine

Reviewing medications for "neuro-pain" when symptoms persist or return

- Review patient's current dose compared to average or typical dose, to ensure an adequate dose for potential problems before adding another medication trial
- If symptoms return, assess for new nociceptive source (UTI, fracture, etc) while considering an increase in a medication dose or the addition of a new medication

Medication	**Problems potentially treated**	**mg/kg/day (weight kg)**	**average or typical dose**
Gabapentin	Central neuropathic pain Dysautonomia Spasticity		30-45 mg/kg/day[3-5] (up to 50-65 mg/kg/day) [3-5]
Clonidine	Spasticity Dysautonomia		0.02 mg/kg/day (range 0.0014-0.15 mg/kg/day)[18]
Baclofen	Spasticity		1.9 mg/kg/day (range 0.14-9.9 mg/kg/day)[18]
Nortriptyline or Amitriptyline	Central neuropathic pain		0.8-1 mg/kg/day[3]

- [3-5]Information about the use of gabapentin in children, including the potential need for 30% higher mg/kg/day dosing in children <5 years of age, up to 50-65 mg/kg/day
- [18]Retrospective review of the use of baclofen and clonidine in the treatment of spasticity
- [3]Option to increase dose above 1 mg/kg/day, see page 8 for further details

Framing information for parents, including why severe impairment of the CNS can cause persistent symptoms (pain, GI symptoms, muscle spasms)

- **Loss of inhibitory control** of the CNS, resulting in severe hypertonia
- **Injury to the spinothalamic tract (central neuropathic pain),** resulting in a lower threshold to symptom generation, which can include pain localized to the GI tract and bladder at times of normal distention of the GI tract and bladder
- **Injury to the areas in the CNS that regulate autonomic control**, with problems including pain and GI symptoms (as described by individuals with dysautonomia)
- **Pain can trigger muscle spasms and severe spasms can be painful**; important to consider both as it is not possible to know which one is primary versus secondary
- **The causes indicated cannot be "fixed" or eliminated**. Medications can decrease symptoms by increasing inhibition or decreasing excitation in the CNS. Most children will have a decrease in symptoms with drug trials, some will not have the degree of benefit desired, and symptoms originating from the CNS can return or persist.

The length of time to continue a medication that is providing benefit

- In young children, continuing the same dose without adjusting for weight gain can indicate ongoing need if symptoms return as the child "outgrows" the dose
- In general, 12 months or longer of symptom control in children with static conditions and stable health may be a reasonable time to consider tapering a medication, being prepared to increase or restart if symptoms return
- Children with diseases or clinical features with neurodegeneration, or with declining health, are likely to benefit from continuation of the medication(s)

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

Consider Pain or Palliative Care Consult (check hospital policy)

Opioid escalation[30]

- 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 at end of life: for pain, dyspnea, agitation, or seizures (end of life symptom treatment not well studied in children)

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 • Continuous infusion: 25-33% of the cumulative loading dose • 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 hour 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	
Phenobarbital	1-5 years 5-12 years >12 years	3-4 mg/kg PO/IV/subcut BID 2-3 mg/kg PO/IV/subcut BID 1-2 mg/kg (50-100 mg) PO/IV/subcut BID For terminal seizures, increase up to 2-4 mg/kg BID

Consult pain or palliative/hospice care teams for assistance, such as when symptoms remain intractable and such interventions are being considered

Transdermal, transmucosal, and rectal medication options

Clonidine: converting between oral and transdermal patch (change every 7 days)
Guideline for converting from oral clonidine to transdermal patch:
Day 1: apply patch, give 100% of oral dose
Day 2: 50% of oral dose
Day 3: 25% of oral dose
Day 4: discontinue oral dose
Converting from transdermal clonidine patch to oral:
Start oral clonidine 8 hours after removing patch (clonidine level is maintained for approximately 8 hours after removing patch and then gradually decreases over several days)

Fentanyl transdermal patch (change every 3 days)
Oral opioid to fentanyl patch: Continue oral opioid for 8-12 hours after fentanyl patch applied and continue prn breakthrough dose (e.g. give short acting opioid when applied then 2 more doses every 4 hours, 3 doses total, along with prn doses as needed)

IV infusion to patch: decrease IV infusion to 50% of the original rate six hours after the application of the first patch, then discontinue twelve hours after application

Fentanyl transmucosal options
Transmucosal lozenge (Actiq), Effervescent buccal tab (Fentora), Buccal soluble film (Onsolis), Sublingual tab (Abstral), Sublingual spray (Subsys), Nasal spray (Lazanda)

Transmucosal Immediate Release Fentanyl Risk Evaluation and Mitigation Strategy: TRIF REMS: when initiating therapy with these products, use the lowest recommended dose and titrate upward according to manufacture instructions and patient response. See website www.TIRFREMSaccess.com

Guidelines for giving antiepileptic drugs rectally[23]

Medication (given at same dose)	Comments
Carbamazepine	• Dilute oral suspension with equal volume of water • Can have a cathartic effect
Lamotrigine	• Crush chewable/dispersible or compressed tablet and mix with 6 mL of room-temperature tap water
Phenobarbital	• Use parenteral solution
Valproic acid	• Dilute oral suspension with equal volume of water • Can have a cathartic effect

Medication toxicities

The most common medication categories to consider include: antidopaminergic (neuroleptics) and SSRIs, paradoxical reactions possible with 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)
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, TCAs, benzodiazepines, antihistamines
Delirium	altered sleep-wake cycle, perceptual and psychomotor disturbances	anticholinergics, TCAs, benzodiazepines, antihistamines

P450 Drug Interaction Table: http://medicine.iupui.edu/clinpharm/ddis/main-table/

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