PALLIATIVE CARE SYMPTOM MANAGEMENT POCKET GUIDE

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PAIN

Basic Principles in Managing Cancer-Related Pain**:**

- Follow the WHO Analgesic Ladder:
  - By the clock: prescribe a **regularly scheduled** dose + **prn** dose for breakthrough pain
  - By the mouth: **oral** route is preferred if able to swallow, otherwise SC/IV/SL/transdermal (avoid intramuscular as this is painful)
  - By the ladder (see below, step 2 no longer valid):
    - Rung 1 **non-opioid** (e.g., acetaminophen, NSAIDs) +/- adjuvant
    - Rung 3 **strong opioid** +/- non-opioid +/- adjuvant
    - Selection should be based on the severity of pain, should start with Rung 3 if severe pain
    - **Adjuvants** include antidepressants, anticonvulsants, corticosteroids (see below)

Basic Principles of Opioid Prescribing**:**

- Half-life: Determines the frequency of **regular** opioid administration
  - q4h for immediate release opioid
  - q12h for sustained release opioid
- Steady state: Determines safe time frame after which you can titrate the **regular** opioid (achieved after 5 half-lives)
  - ~24h (daily) for immediate release opioid
  - ~72h (every 3 days) for sustained release opioid
- Time to peak effect: Determines the frequency of **prn** opioid administration; dependent on route (see table below)
- Breakthrough dose: Usually ~10% of total daily dose of routine opioid
- Use the **same drug** for the routine and prn opioid (unless using transdermal Fentanyl patch for the regular opioid, then must use morphine, hydromorphone, or oxycodone for breakthrough pain)

ROUTINE OPIOID ADMINISTRATION FOR PAIN CONTROL		
ROUTE	**FREQUENCY OF ROUTINE DOSE**	
PO/SC/IV – immediate release	q4h	
PO – sustained release	q12h (rarely q8h); q24h if using Kadian	
PRN OPIOID ADMINISTRATION FOR BREAKTHROUGH PAIN		
ROUTE	**TIME TO PEAK EFFECT**	**FREQUENCY OF PRN DOSE**
PO	60-90 minutes	q1h
SC	30-60 minutes	q1h
IV	10-20 minutes	q30min

MILD PAIN: ESAS PAIN SCORE 1-3/10

Treatment with Non-Opioids

- Consider acetaminophen and/or NSAIDs (discontinue if lack of significant effect after 1 week)
- Add PPI with long term NSAID use

Treatment with Opioids

- May consider using very low dose opioids in combination with non-opioid agents

MODERATE PAIN: ESAS PAIN SCORE 4-6/10

Opioid Naive (choose 1 of the following opioids)

- Morphine 5mg PO q4h and 2.5mg PO q1h prn for breakthrough pain (consider 2.5mg PO q4h in the frail/elderly)
- Hydromorphone 1mg PO q4h and 0.5mg PO q1h prn for breakthrough pain (consider 0.5mg PO q4h in the frail/elderly)
- Oxycodone 2.5mg PO q4h and 2.5mg PO q1h prn for breakthrough pain

Patients Already on Opioids

- Increase the routine (immediate release or sustained release) opioid dose by 25% or titrate based on total amount of opioid used in the last 24 hours (taking into account both routine and prn doses)
- Continue to dose the breakthrough opioid as 10% of the new total daily dose of the routine opioid

*Note: For ease of administration, convert from PO immediate release (dosed q4h) to PO sustained release formulation (dosed q12h) once pain is well controlled

SEVERE PAIN: ESAS PAIN SCORE 7+/10

Opioid Naive (choose 1 of the following)

- Morphine 5-10mg PO q4h and 5mg PO q1h prn for breakthrough pain

OR

- Morphine 2.5-5mg SC q4h and 2.5mg SC q1h prn for breakthrough pain
- Hydromorphone 1-2mg PO q4h and 1mg PO q1h prn for breakthrough pain

OR

- Hydromorphone 0.5-1mg SC q4h and 0.5mg SC q1h prn for breakthrough pain

Patients Already on Opioids

- Increase the routine (immediate release or sustained release) opioid dose by 25% or titrate based on total amount of opioid used in the last 24 hours (taking into account both routine and prn doses)
- Continue to dose the prn breakthrough opioid as 10% of the new total daily dose of the routine opioid

*Note: If patient is prescribed a sustained release opioid and experiencing severe pain, use clinical judgment and consider switching back to immediate release to allow for more rapid titration; also consider switching from PO to SC route for a more rapid time to effect

PAIN CRISIS [SEVERE PAIN UNRESPONSIVE TO CURRENT REGIMEN]

Opioid Naive

- No IV access – stat morphine 5-10mg SC q30 minutes until pain relieved (or hydromorphone 1-2mg SC)
- IV access – stat morphine 5-10mg IV q10 minutes until pain is relieved (or hydromorphone 1-2mg IV)

Already on Opioids

- No IV access - give the PO prn dose quantity as SC q30 minutes until pain is relieved
- IV access – give the PO prn dose quantity as IV q10 minutes until pain is relieved

*Note: May consider doubling the dose if lack of effect seen after 2 doses (use clinical judgement and monitor for respiratory depression)

- Once pain is reduced to an appropriate level, restart a routine opioid given q4h based on the total usage in the last 24hr (including doses given during pain crisis) using clinical judgement, and provide breakthrough dose based on 10% of the total daily dose of routine opioid

EQUIANALGESIC DOSING OF OPIOIDS		
DRUG	**ROUTE**	
	PO	**SC/IV**
Morphine	10mg	5mg
Codeine	100mg	--
Oxycodone	7.5mg	--
Hydromorphone	2mg	1mg
EQUIANALGESIC DOSING OF FENTANYL		
Fentanyl 25mcg/hr patch ~= 60mg of PO morphine in 24 hr		
EQUIANALGESIC DOSING OF METHADONE		
Consult palliative care or a reference manual; complex and non-linear Relationship		

NOTE: Reduce equianalgesic dose of new opioid by ~25% when rotating opioids for reasons other than opioid toxicity to account for incomplete cross-tolerance between opioids.

Opioid Toxicity:

- **Signs and Symptoms:** Confusion, delirium, hallucinations, restlessness/agitation, myoclonus, seizures, hyperalgesia
- **Treatment:**
  - IV/SC hydration (enhances renal clearance of opioid)
  - Reduce opioid dose OR rotate the opioid and reduce the dose of the new equianalgesic opioid by ~50% (using clinical judgement) to account for incomplete cross tolerance

Opioid Overdose:

- **Signs and Symptoms:** Sedation, pinpoint pupils, decreased respiratory rate (RR)
- **Treatment:**
  - If RR <8, check if patient is rousable, if they are then consider careful monitoring and hold next opioid dose
  - If RR <8 and unrousable, dilute naloxone 0.4mg/ml with 9ml of NS and give 1ml (0.04mg) q5-10 minutes until RR >8 and sedation reducing (if the full dose of naloxone is given, may precipitate a pain crisis)

OPIOID FORMULATIONS		
Drug	**Formulations**	
Codeine	Tylenol #1, #2, #3, #4: 325mg Tylenol +8, 15, 30, 60mg of codeine respectively Codeine Contin: 50mg, 100mg, 150mg, 200mg	
Morphine	IR	5mg, 10mg, 20mg, 25mg, 30mg, 40mg, 50mg, 60mg
	SR	10mg, 15mg, 30mg, 60mg, 100mg, 200mg* **Kadian is q24hr: 10mg, 20mg, 50mg, 100mg
Hydromorphone	IR	1mg, 2mg, 4mg, 8mg
	SR	3mg, 4.5mg, 6mg, 9mg, 12mg, 18mg, 24mg*, 30mg*
Oxycodone (EAP or Palliative MD for coverage except Percocet)	IR	5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg
	SR	10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg
Fentanyl patch (Transdermal) (LU code 511 - need to have tried other SR opioid 1st)	12mcg/hr (not covered), 25mcg/hr, 50mcg/hr, 75mcg/hr*, 100mcg/hr* Not recommended to cut or cover patches with occlusive dressings like Tegaderm; may lead to unpredictable drug absorption levels	

Note: IR = immediate release; SR = sustained release

* = these high doses are only covered by ODB when prescribed by physicians with 'palliative care facilitated access' (PCFA)

NEUROPATHIC PAIN - ADJUVANT AGENTS

Consider both medication side effect profile and efficacy when choosing most appropriate agent. There is poor evidence for the efficacy of adjuvants in chemotherapy-induced neuropathic pain.

DRUG CLASS	DRUG / DOSE	ADVERSE EFFECTS	NOTES
FIRST LINE Tricyclic antidepressants(TCAs) NNT = 3.6 NNH = 13.4	**Nortriptyline** -Start at 10-25mg PO qhs -Max 150mg/day -Titrate slowly to effect by 25mg/day **Amitriptyline** -Start at 25mg PO qhs (Start with 10mg in frail/elderly) -Max 150mg/day -Titrate slowly to effect by 10-25mg/day	Orthostatic hypotension, QT prolongation, dizziness, drowsiness, anticholinergic side effects	- Less anticholinergic side effects with nortriptyline - Caution in patients with glaucoma, prostatic hypertrophy,CVD - Consider for pain described as *burning*
FIRST LINE Anticonvulsants Gaba NNT 6.3 NNH 25.6 Pregab NNT 7.7 NNH 13.9	**Gabapentin** -Start at 100mg PO TID -Max 3600mg/day -Titrate upward to effect q2-3 days **Pregabalin** -Start at 75mg PO bid (or 50mg PO bid in sensitive individuals) -Titrate to effect q5-7 days -Max 600mg/day Note: Doses >300mg/day rarely more effective	Dizziness Somnolence Blurred vision Dyscoordination Somnolence Peripheral edema	- Renal dosing required - Renal dosing required
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	**Venlafaxine** -Start at 37.5mg PO once daily -Titrate to effect by37.5mg qweekly -Max 225mg/day	May cause sustained increasein BP, tachycardia,insomnia, drowsiness, dizziness, nausea, diaphoresis, constipation	- Renal and hepatic dosing required - Caution with history of seizure disorder

NNT = 6.4 NNH = 11.8	**Duloxetine** -Start at 30-60mg PO once daily -Max 120mg daily -Note: doses > 60mg daily rarely more effective -Some evidence for chemotherapy-induced neuropathic pain	Sedation Nausea Constipation Ataxia Dry mouth Seizures	- Avoid use if CrCl < 30ml/min - Contraindicated in hepatic impairment - Caution in patients with seizure disorder or predisposition to seizures

- **Malignant Bone Pain – Adjuvant Therapies**
  - Steroids, NSAIDs, possibly bisphosphonates
  - Radiation therapy, surgery (vertebroplasty, kyphoplasty)
- **Severe Pelvic Pain Secondary to Underlying Malignancy**
  - Consider neuro-axial interventions such as epidural orintrathecal by anaesthesia
- **Other:** Lidocaine, ketamine – consult with palliative medicine specialist

DYSPNEA

- Appropriately titrated opioids do not cause persistent respiratorydepression in patients with dyspnea
- Benzodiazepines are not recommended for the treatment ofdyspnea (but may be used for associated anxiety)
- Supplemental oxygen is not recommended for dyspneic patientswho are not hypoxic
- Palliative care patients may receive funded home oxygen therapy for a limited period (90 days) once considered "palliative"
- Medical eligibility for funded home oxygen therapy for non-palliative patients:
  - Chronic hypoxemia at rest ($PaO_2 \leq 55$mmHg or $SpO_2 \leq 88\%$)
  - PaO_2 56-60mmHg (SpO_2 89-90%) on room air and any of the following: pulmonary HTN, cor pulmonale, erythrocytosis, exercise limited by hypoxemia that improves with supplemental oxygen, nocturnal hypoxemia
- **Treat the Underlying Cause if Possible**
  - COPD – inhaled bronchodilators, inhaled steroids, systemicsteroids
  - Airway obstruction – steroids, radiation therapy
  - Pleural effusion – thoracentesis, PleurX catheter insertion, talcpleurodesis
  - Pneumonia – antibiotics
  - Pulmonary embolism – anticoagulation, IVC filter
  - Angina, atrial fibrillation, CHF – optimize cardiac meds
  - Pericardial effusion – pericardiocentesis, pericardial window,sclerosing agent
  - SVC obstruction – systemic steroids, radiation therapy
  - Anemia - transfusion of PRBCs
  - Ascites – paracentesis, indwelling intraabdominal catheter ifrecurrent
  - Constipation – optimize laxative use

MILD DYSPNEA: ESAS DYSPNEA SCORE 1-3/10

Non-Hypoxic (O_2 > 90%)
- Use fan, humidified air via nasal prongs
- If not effective, consider trial of humidified supplemental oxygen via nasal prongs (discontinue after several days if no benefit)
- Discuss energy conservation techniques, pursed lip breathing, relaxation techniques
- Blowing fan directly or tangentially on the face

Hypoxic (O_2 < 90%)
- Humidified supplemental oxygen with flow rate 1-6L/minute
- Target reduction in dyspnea or oxygen saturations > 90% (if not a CO_2 retainer)
- Consider using oxymizer, ventimask, or non-rebreather mask if dyspnea/low oxygen saturations persist

Pharmacologic agents
- Consider systemic opioids if non-pharmacologic strategies ineffective
- Consider opioids for continuous dyspnea (not exertional dyspnea – time to onset will limit potential benefit)
- If already on an opioid, titrate appropriately

MODERATE DYSPNEA: ESAS DYSPNEA SCORE 4-6/10

Opioid -Naive Patients
- Morphine 2.5-5mg PO q4h routine and 2.5mg PO q2h prn for breakthrough dyspnea (or another immediate release opioid at an equivalent dose)
- If unable to give PO, morphine 2.5mg SC q4h routine and 1.5mg SCq1h prn for breakthrough dyspnea

Patients Already on Opioids
- Increase regular dose by 25% or titrate based on breakthrough use inthe last 24h
- Breakthrough dose = 10% of total daily dose of routine opioid
- Oral breakthrough frequency = q2h prn
- SC breakthrough frequency = q1h prn

- Consider trial of methotrimeprazine if dyspnea is persistent: 2.5-10mg PO/SC q6-8h routine or prn

SEVERE DYSNPEA: ESAS DYSPNEA SCORE 7-10/10

Opioid - Naive Patients

- Morphine 2.5mg SC/IV bolus (or another immediate release opioid at an equivalent dose) q30min prn
- Consider doubling the dose if 2 doses fail to produce appropriate reduction in dyspnea
- Monitor respiratory rate (note time to peak effect of SC opioid may take longer than 30min)

Once dyspnea is reduced to an appropriate level, restart an immediate release routine opioid given q4h based on the total usage in the last 24hr (including bolus doses) using clinical judgement, and provide breakthrough dose based on 10% of the total daily dose of routine opioid (consider using SC route for routine and prn doses until symptoms controlled)

Patients Already on Opioids

- Give a SC/IV bolus equal to 10% of the total daily dose of the routine opioid
- Increase the regular opioid by 25% or based on total number of boluses used once dyspnea is controlled

Consider trial of methotrimeprazine if dyspnea persistent or associated anxiety
-2.5-10mgPO/SC q6-8h routine or prn

Midazolam may also be considered if significant anxiety is associated
-0.5-1mg SC q30min PRN (*may need higher doses if dyspnea crisis)

*Note: no role for nebulized opioids

DYSPNEA CRISIS [SEVERE DYSPNEA NOT RESPONSIVE TO OPIOIDS]

As above (for severe dyspnea), but may require proportionate palliative sedation with benzodiazepines [e.g. midazolam] for severe distress and air hunger. Opioids to be continued, oxygen support for hypoxia.

Inhalers

Consider a trial of a different formulation if patient has poor response to a particular inhaler. Some patients do better with nebulized administration versus MDIs, although MDIs generally preferred.

SHORT-ACTING BRONCHODILATORS (Relievers)		
Salbutamol (Ventolin HFA)	β2 agonist	100mcg
Salbutamol (Ventolin Diskus)	β2 agonist	200mcg
Terbutaline (Bricanyl Turbuhaler)	β2 agonist	0.5mg
Ipratropium (Atrovent HFA)	Anticholinergic	20mcg
LONG-ACTING BRONCHODILATORS (Controllers)		
Salmeterol (Serevent Diskus)	Long-acting β2 agonist	50mcg
Formoterol (Oxeze Turbuhaler)	Long-acting β2 agonist	6mcg, 12mcg
Indacaterol (Onbrez)	Long-acting β2 agonist	75mcg
Tiotriopium (Spiriva Handihaler)	Long-acting anticholinergic	18mcg
Aclidinium (Turdoza Pressair)	Long-acting anticholinergic	400mcg
Glycopyrronium (Seebri Breezhaler)	Long-acting anticholinergic	50mcg
LONG-ACTING INHALED CORTICOSTEROIDS (Controllers)		
Fluticasone (Flovent HFA)	50mcg, 125mcg, 250mcg	
Fluticasone (Flovent Diskus)	50mcg, 100mcg, 250mcg, 500mcg	
Budesonide (Pulmicort Turbuhaler)	100mcg, 200mcg, 400mcg	
Beclomethasone (Qvar)	50mcg, 100mcg	
Ciclesonide (Alvesco)	100mcg, 200mcg	
COMBINATION MEDICATIONS (LONG-ACTING BRONCHODILATORS AND LONG-ACTING INHALED CORTICOSTEROIDS) (Controllers)		
Formoterol/Budesonide (Symbicort Turbuhaler)	6/100mcg, 6/200mcg	

Salmeterol/Fluticasone (Advair MDI)	25/125mcg, 25/250mcg
Salmeterol/Fluticasone (Advair Diskus)	50/100mcg, 50/250mcg, 50/500mcg
Formoterol/Mometasone (Zenhale)	5/100mcg, 5/200mcg
Vilanterol/Fluticasone (Breo)	25/100mcg LU code 456 – long term treatment of patients with mod-severe COPD with frequent acute exacerbations and inadequate response to long acting bronchodilator alone

Note: N-acetyl cysteine (NAC) supplement is used as a mucolytic agent in COPD to decrease sputum volume. Starting dose 600mg PO daily to bid.

COUGH

- Identify/treat reversible causes if possible and within goals of care e.g:
  - Dexamethasone 2-16mg PO daily for conditions such as lymphangitic carcinomatosis, treatment pneumonitis, or airway obstruction caused by tumour
  - Inhalers for COPD or asthma
  - PPI or H2 blocker for GERD
  - Nasal corticosteroid for post-nasal drip
  - Antibiotics for bacterial pneumonia
  - Anticoagulants for pulmonary embolism
  - Thoracentesis for pleural effusion
  - Medication-induced cough (e.g. ACE-inhibitor related)
- Reduce environmental triggers, smoking cessation if possible
- Non-pharmacological interventions:
  - Dry cough: positioning, speech therapy strategies, humidifier
  - Productive cough: Airway clearance (chest PT), nebulized saline (0.9% or 3%) 5ml nebulized q4h prn
- Pharmacological interventions:
  - Dextromethorphan 15-30mg PO q4h PRN
  - Low dose opioids PO q4h PRN
  - Lose dose methadone (1mg PO q12h)
  - Lidocaine solution (2%) 2-5ml nebulized q4h PRN (keep NPO for 1 hour after use)
  - Gabapentin (malignant cough) 100-300mg PO BID
  - Paroxetine 10-20mg PO daily
  - Guaifenesin 200-400mg PO q4h PRN (thick phlegm) *do not use in patients who cannot cough*
  - N-Acetylcysteine 600mg PO or nebs BID (thick phlegm)

NAUSEA & VOMITING

- Assessment: look for dehydration, jaundice, infection, signs of cranial lesion
- Possible investigations: blood work (CBC, calcium, glucose, renal and liver function), abdominal x-ray/ultrasound/CT, CT head
- Possible causes: gastric stasis and chemical disturbance are the most common but often multifactorial
    - Chemical
    - Cortical
    - Cranial
    - Vestibular
    - Gastric stasis
- Non-pharmacological management:
    - Good oral care, watch for thrush, prevent constipation
    - Baking soda ($NaHCO3$) mouth rinses after vomiting
    - Small, frequent meals
    - Eliminate strong odors
- Pharmacological management:
    - Oral route if possible but may need IV/SC if vomiting
    - Choice of drug depends on presumed underlying etiology and the pathways as well as receptors involved
    - Use first line drug and monitor for 48 hours; if symptoms persist, consider different antiemetic or addition from another class

	SITE	CONTRIBUTING FACTORS	RECEPTORS TO TARGET/DRUGSTO CONSIDER
VOMITING CENTRE (VC)	Chemoreceptor Trigger Zone (CTZ) – located in the area postrema on the floor of the 4th ventricle	CHEMICAL – BLOOD & CSF Drugs, toxins, metabolic causes (DKA, uremia)	Dopamine (D2) Serotonin (5HT3)
	Vagus and Sympathetic Afferent Nerves	VISCERAL ABDOMINAL ORGANS GI irritation, distention, motility disorder, obstruction, stasis, carcinomatosis	D2, 5HT4(+) 5HT3 Histamine (H1)
	Vestibular Apparatus	Cerebellar tumor, motion, Meniere's Disease	H1 Muscarinic (M)
Receptors: 5HT2,5HT3, H1, M, CB1 NK1	Cerebral	INCREASED ICP Brain mets, bleeding, edema, meningitis	Dexamethasone
		PSYCHOLOGICAL Sights, smells, tastes	Benzodiazepines, nabilone, psychological relaxation strategies

DRUG / DOSE	MECHANISM AND SITE OF ACTION	SIDE EFFECTS AND NOTES
Metoclopramide (Metonia) ** **Pall care preferred med** ** 5-10mg PO/SC/IV QID (ac meals and qhs) + q4h prn Max dose 60mg/day	D2 antagonist GI tract and CTZ 5HT3 antagonist (at high doses >120mg/day) GI tract 5HT4 agonist (promotility action)	- Works on upper GI tract and small bowel - Risk of EPS - QT prolongation - Avoid in complete bowel obstruction
Domperidone (Motilium) 5-10mg PO TID Max dose 30mg/day	D2 antagonist GI tract and CTZ	- Does not cross BBB, less risk of CNS side effects - QT prolongation
Haloperidol (Haldol) 0.5-1 PO/SC/IV BID + q4h prn Max dose 20mg/day	D2 antagonist GI tract and CTZ	- Risk of EPS - QT prolongation - Little sedating effect
Prochlorperazine (Stemetil) 5-20mg PO/SC/IV q4-6h prn Max dose 60mg/day	D2 antagonist GI tract andCTZ Anticholinergic VC, Vestibular apparatus	- Risk of EPS reactions and hypotension - QT prolongation

Methotrimeprazine (Nozinan) 2.5-25mg PO/SC q4-6h prn Max dose 300mg/day	D2 antagonist GI tract and CTZ H1 antagonist VC Anticholinergic VC Cerebral cortex	- Risk of EPS, drowsiness, orthostatic hypotension - QT prolongation (Rare) -Reduces seizure threshold
Ondansetron 4-8mg PO (tablet or ODT)/SC/IV q8h prn Max dose 24mg/day	5HT3 Antagonist GI tract and CTZ and VC	- Useful in chemotherapy induced nausea and vomiting - Expensive - Risk of constipation and prolonged QTc
Dimenhydrinate 12.5-100mg PO/SC/IV q4-6h prn Max dose 400mg/day	H1 antagonist VC, vestibular apparatus	- Risk of drowsiness, dry mouth, constipation, confusion in the elderly
Hyoscine transdermal patch or SC (Scopolamine) One or two 1.5mg patches applied transdermally q72h OR 0.3-0.6mg SC q4h	Anticholinergic VC, Vestibularapparatus	- Risk of confusion, sedation, agitation and hallucinations
Lorazepam 0.5-2mg PO/SL/SC/IV q4-6h prn Max dose 8mg/day	Anxiolytic Used for anticipatory nausea	- Risk of drowsiness, lethargy, confusion

Nabilone 0.5-1mg PO BID Max dose 6mg/day	CB1 agonist VC	- Risk of disorientation, drowsiness, hallucinations, behavioural changes, dysphoria, tachycardia, anxiety, dry mouth
Dexamethasone 2-8mg PO/SC/IV qam Max dose 16mg/day	Unknown (felt to be related to reducing sensitivity of CTZ to ematogenic irritants +/- reducing inflammatory mediators)	- Risk of confusion, psychosis, insomnia, fluid retention, GI irritation, hyperglycemia - Used in refractory cases, mechanical bowel obstruction, elevated ICP
Olanzapine 2.5-10mg PO/SC qhs or bid, or q8h prn Max dose 30mg/day	D2 antagonist CTZ 5HT2 antagonist VC	- Role in refractory cases - Risk of EPS

Note: Nabilone, steroids, and benzodiazepines are the only medications that don't prolong QTc

Chemical causes (e.g., drugs, chemotherapy, hypercalcemia, infection)	1st line: haloperidol or metoclopramide 2nd line: olanzapine 3rd line: methotrimeprazine
Cortical causes (e.g., anxiety, pain, emotional factors)	1st line: lorazepam 2nd line: methotrimeprazine
Cranial causes (e.g., raised ICP, leptomeningeal disease)	1st line: dexamethasone or dimenhydrinate
Vestibular causes (e.g., motion sickness, vertigo, tumor)	1st line: dimenhydrinate 2nd line: scopolamine
Gastric stasis causes (e.g., opioids, autonomic dysfunction)	1st line: metoclopramide 2nd line: domperidone

CONSTIPATION

- First line agents: Oral laxatives
  - Osmotic laxatives: PEG 3350, Lactulose
  - Stimulant laxatives: Sennosides, Bisacodyl
- Second line: Rectal interventions (continue oral laxatives)
  - Suppositories (glycerin, bisacodyl)
  - Enemas (sodium phosphate, tap water, mineral oil)
  - Avoid DRE/rectal interventions in patients with neutropenia or thrombocytopenia due to risk of infection/bleeding
  - Refractory opioid-induced constipation: Methylnaltrexone
  - Consider only when optimal dose of regular laxatives are ineffective for opioid-induced constipation. Very rarely required and use is restricted within our hospital to palliative MDs
- Note: No role for docusate in the management of constipation in the palliative care population
- Note: During the last hours/days of life when patients are unable to receive PO medications, PO laxatives should be discontinued. The need for ongoing bowel care is rare at this stage.

DRUG AND FORMULATIONS	DOSE	ONSET OF ACTION	NOTES
STIMULANT LAXATIVES			
Sennosides 8.6mg tablets 8.8mg/5ml solution	Start at 1-2 tabs (8.6-17.2mg) PO qhs Titrate up to 4 tabs (34.4mg) bid as needed	8-12h	- Causes colonic peristalsis by stimulating the myenteric plexus - Often used for opioid induced constipation
Bisacodyl 5mg tablets	Start at 2-4 tabs (10-20mg) PO qhs Titrate up to 4 tabs(20mg) tid as needed	6-12h	
OSMOTIC LAXATIVES			
Lactulose	15-60ml divided od-tid (max 120ml perday)	1-3 days	- Can cause abdominal cramping, bloating, flatus - Sweet taste may be poorly tolerated
PEG 3350 (Polyethylene Glycol)	17grams (1 capful; 1 packet) of powder dissolved in 120 to 240ml of fluid od - tid	1-3 days	- Often better tolerated than lactulose - Not covered by ODB
SUPPOSITORIES			
Glycerin Suppository	1 suppository PR	15-60min	- Softens stool in the rectum
Bisacodyl Suppository	10mg suppository PR	20-180min (mean 1hr)	- Induces peristalsis
ENEMAS			

Sodium Phosphate Enema (Fleet® enema)	1 enema (130ml) PR	15min	- Osmotic and peristaltic agent - Avoid in neutropenia - Prolonged use can cause hypocalcemia - Caution with renal failure (contains Mg & phosphate) - Does not workhigher than the rectum
Mineral Oil Retention Enema	120ml PR	1hr	- Avoid in neutropenia - Softens impactedstool higher up from the rectum
High Tap Water Enema	Volume from 250-1000mL.	20mins (Hold if possible)	- Useful when fecal loading is above
PERIPHERALLY ACTING MU OPIOID RECEPTOR ANTAGONISTS			
Methylnaltrexone (Relistor ®)	Weight-based: 8mg SC x 1 if 38-62kg 12mg SC x 1 if 62-114mg Repeat q24h x2 days if no bowel movement Renal dosing required in renal failure	Usually within 4 hr	- Antagonizes opioids at GI μ opioid receptors, unable to cross BBB thus does not impair analgesia - Contraindicated if bowel obstruction, predisposition to perforation - Expensive, not covered by ODB
Naloxegol (Movantik®)	12.5 - 50 mg p.o. daily	6-12 hr	- Expensive, not covered by ODB - Multiple drug interactions (CYP3A4) - Contraindicated if bowel obstruction, predisposition to perforation

DIARRHEA

- **Etiology:**
  - Drugs – Laxatives (common cause in palliative setting), chemotherapy (e.g. 5-FU, irinotecan, capecitabine), antibiotics, magnesium
  - Constipation - Fecal impaction with "overflow diarrhea"
  - Infection – Viral/bacterial gastroenteritis, C. difficile, HIV-associated (CMV, Cryptosporidia, E. hystolytica, etc.)
  - Tumor – Carcinoid, pancreatic islet cell tumor, colon and rectalcancer, partial bowel obstruction
  - Radiation – Radiation-induced enteritis (especially after abdominal/pelvic RT)
  - Malabsorption – Pancreatic insufficiency, post-surgical (e.g. ileal resection, colectomy)
  - Comorbid illness – hyperthyroidism, IBD, IBS, etc.
- **Management depends on etiology!**
- **General Non-Pharmacological Measures**
  - Hold laxatives unless concern for constipation with overflow diarrhea
  - Small, frequent meals with consumption of soluble fibre
  - Limit consumption of fatty foods, caffeine, spice, dairy, insoluble fibre
  - Oral hydration to prevent dehydration
  - Depending on symptom severity, may require IV hydration, electrolyte replacement
  - Perineal skin care with barrier cream prn to prevent skin breakdown

DRUG AND FORMULATION	DOSE	MECHANISM OF ACTION AND NOTES
Loperamide 2mg tablets	4mg PO x 1, then 2mg PO after each loose BM(max 16mg/day)	- Peripheral mu opioid receptor agonist, does not cross BBB so minimal systemic side effects - 1st choice for non-infectious diarrhea ****Avoid if risk of infectious cause****
Octreotide	Initial dose 100-150 mcg SC TID	- Multiple mechanisms including reduced VIP release, decreased gut motility - Used for refractory diarrhea, carcinoid syndrome, VIP-secreting tumours, or high-output stoma
Cholestyramine	Initial dose 4 g (1 packet) daily	- Bile acid sequestrant - Used for diarrhea from radiation-induced enteritis or diarrhea due to ileal resection/bypass
Pancreatic enzymes (Creon®)	Variable, depends on fat intake	- Used for steatorrhea secondary to pancreatic insufficiency
Antibiotics	Per antibiotic dosing	- For treatment of infectious diarrhea (C. Difficile, Shigella, Salmonella, etc.)

PRURITUS

- **Common Etiologies:**
  - Cholestasis
    - Pathogenesis not certain, postulated central and peripheral mechanisms (note: pruritus does not correlate well with bile acid levels)
    - Pattern: Starts on hands/feet, may have hyperpigmentation at mid-back, may be more intense at night
  - Uremia
    - Multifactorial, secondary to accumulation of pruritogenic metabolites, secondary hyperparathyroidism, mast cell proliferation, etc. Dry skin very common.
    - Pattern: Generalized or localized.
  - Malignancy related
    - Multiple mechanisms, may be paraneoplastic related to cytokine imbalance, or localized at site of tumour
    - Pattern: Generalized pruritus may be an early symptom of a solid tumor vs localized pruritus may be associated with aspecific tumor (prostate – scrotal pruritus; uterine/cervix – vulvar pruritus; rectum – anal pruritus). Generalized pruritus common in myeloproliferative disorders (polycythemia vera – 50%, Hodgkin lymphoma – 30%)
  - Opioids
    - Multiple proposed mechanisms including mu-opioid receptor activation of serotonin pathways, histamine release from mast cells
    - More common with intrathecal administration, occurs in only 1% with PO/SC/IV route
- Management:
  - General skin care measures +/- topical therapies for everyone
  - If persistent or severe, generalized, consider systemic agents

- **General Skin Care:**
  - Lukewarm baths (may add baking soda)
  - Apply fragrance-free emollient moisturizer immediately after bathing
  - Avoid irritants and fragrances
  - Wear loose cotton clothing
  - Cool, humidified air
  - Tap water wet dressings may provide temporary relief
- **Disease-directed Non-Pharmacologic Interventions:**
  - Consider biliary stenting with obstruction (i.e. pancreatic cancer leading to cholestasis)
  - UV light therapy effective for uremia, cholestasis, and malignant skin infiltration – functional status may limit use. Reduces the number of nerve endings and mast cells in the skin
- **TOPICAL TREATMENTS**
  - Lubricants for Dry Skin:
    - Unscented emollient / moisturizing creams available over the counter (lotions may not be thick enough)
  - Cooling Agents:
    - Camphor (0.5 - 2%) or menthol (1%) compounded preparations
    - Combination menthol, camphor, pramoxine in Glaxal base
    - Pramoxine (1%) and calamine (3%) (= Aveeno® Anti-itch Lotion)
  - Capsaicin 0.025%-0.075% (Zostrix®):
    - Apply bid and titrate up to tid-qid as needed
    - Weak evidence. Adverse effects include burning sensation, hyperalgesia
  - Lidocaine cream 2.5%: Consider for localized pruritus
    - Caution re: systemic absorption with excess amounts
    - Apply thin film to affected area 2-3x daily
  - Topical corticosteroids: Consider only if associated inflammation
    - Hydrocortisone 1% - mild potency
    - Betamethasone valerate 0.1% - moderate potency
- **SYSTEMIC TREATMENTS:**

- Treatment differs based on cause (see table)
- For general pruritus in palliative care, consider:
  - Antidepressants (E.g. Paroxetine, sertraline, mirtazapine)
  - Gabapentinoids (Pregabalin, gabapentin)

PHARMACOLOGIC MANAGEMENT:

DRUG / DOSE	INDICATION	SIDE EFFECTS	NOTES
Paroxetine Starting: 5-10mg PO qhs Increase by increments of 10mg q4-5 days prn Max dose 20mg PO once daily	Cholestasis Uremia Opioid-induced Malignancy	N/V (initially)	- Effect seen within 24-48h - Beneficial in palliative care patients with pruritus secondary most causes
Mirtazapine Starting: 7.5mg - 15 mg PO qhs Increase if needed by 15mg PO qhs after 1 week Max dose 30mg/day	Cholestasis Uremia Opioid-induced Malignancy	Sedation Increased appetite Weight gain	- Onset of action 1-7 days - Consider if prominent sleep disturbance secondary to pruritus
Sertraline Starting: 25 mg PO daily May uptitrate by 25 mg every 5-7 days	Cholestasis Uremia Opioid-induced	Insomnia Nausea	
Gabapentin or Pregabalin 100-300mg (gabapentin), 25- 75mg (pregabalin) after dialysis or daily	Uremia Opioid-induced Malignancy	Fatigue Somnolence Dizziness	- Renal dosing required

Naltrexone 6.25 - 12.5 mg PO daily	Cholestasis Uremia Opioid-induced	Headache Insomnia Dizziness N/V Reduced appetite Diarrhea	- Risk of precipitating opioid withdrawal and reversal ofanalgesia - Onset of action < 48h
Ondansetron Starting: 4mg PO/SC/IV BID-TID Max dose 8mg PO/SC/IV TID	Opioid-induced	Constipation Headaches	- Lack of evidence for benefit in uremia, cholestasis
Cholestyramine Starting: 4gm PO 30min before and 30min after breakfast (add pre/post lunch OR dinner if needed) Max dose 16g/day	Cholestasis Uremia Solid tumours	Nausea Diarrhea Numerous drug interactions (take 4h after other medications)	- Onset of action approx. 2 weeks

Note: Histamine does not typically contribute to pruritus in palliative care patients. Thus, anti-histamines are not usually beneficial. Benefits secondary to antihistamines may relate to sedating effects.

HICCUPS

- Lasting < 48h = acute; >48 h = persistent
- **Differential Dx:**
  - Vagus nerve irritation: **Gastric stasis / distension** (common), GERD, peptic ulcer disease, esophagitis, pericarditis, etc.
  - Diaphragmatic irritation: Pleural/subphrenic inflammation or infection, hepatomegaly, malignancy with local invasion of diaphragm, ascites, hiatus hernia, etc.
  - Metabolic/toxic etiology: Uremia, infection, hypercalcemia, hypomagnesemia, etc.
  - Tumor of the CNS: increased ICP
  - Drugs: Steroids (especially dexamethasone), barbiturates, benzodiazepines, certain chemotherapy agents
- Approach to Treatment:
  - Treat the underlying cause if known
  - Attempt non-pharmacologic maneuvers, such as:
    - Breath holding x 5-10 seconds
    - Valsalva
    - Sipping cold water
  - If persistent (>48h), consider pharmacologic interventions

DRUG/DOSE	MECHANISM OF ACTION	SIDE EFFECTS / NOTES
Proton Pump Inhibitor Variable	Inhibits gastric acid secretion	Generally well tolerated Use if GERD suspected
Baclofen Starting dose 5-10 mg PO TID Maximum 45 mg/day	Enhances inhibitory effect of GABA	Ataxia, dizziness, delirium, sedation. May not be tolerated in the elderly. Risk of withdrawal symptoms if discontinued abruptly.
Gabapentin Starting dose 100-300 mg PO TID Usual maximum 1200 mg/day	Blocks calcium channels and increases GABA which may modulate diaphragmatic excitability	Drowsiness, ataxia, dizziness, peripheral edema
Chlorpromazine Starting dose 25-50mg PO/SC/IV q6h	Dopamine antagonist Only medication with approved indication for hiccups	Hypotension, urinary retention, drowsiness, delirium, EPS, glaucoma
Metoclopramide Starting dose 5-10mg PO QID	Dopamine antagonist	EPS

MOUTH CARE

– **Non-Pharmacological General Principles of Oral Care**
– RINSING:
    - Removes debris, maintains moisture, removes toothpaste,reduces risk of infection, neutralize mouth after emesis
    - Bland rinse recommended: 1 tsp salt + 1 tsp baking soda + 1L of water (prepare daily, do not refrigerate)
    - Avoid: Alcohol based mouth washes and club soda (acidic)
– MOISTURIZING:
    - Water, artificial saliva (e.g. Moi-Stir Spray, Biotene products)
    - Avoid glycerine/lemon swabs (ineffective, can cause drymouth)
    - Xylitol gum/lozenges (up to 6 gm per day) can stimulate saliva
    - Apply lubricant after each cleaning, bedtime, and prn
– **Pharmacological Oral Care**
    - **PAIN MANAGMENT (Oral Mucositis)**
        - Rule out pain from canker sores, herpetic lesions, oral thrush
        - **Opioids** are the systemic treatment of choice
            - Give PO opioid 30-60 min prior to eating or brushing teeth prn.
        - Apply topical anesthetic mouthwash 10min before eating/brushing teeth
            - Viscous **lidocaine** 2%: 15ml swish + spit (or swallow) up to q3h prn (Avoid eating within 1 hour if swallowing)
    - **EXCESSIVE SECRETIONS**
        - **Tricyclic Antidepressants** (start low and titrate prn)
        - **Scopolamine** transdermal patch 1.5mg topically q72h
        - End of life - See Oropharyngeal secretions in End Of Life section
    - **THICK SECRETIONS**
        - Nebulized saline
    - **DRY MOUTH (Xerostomia)**
        - Rule out oral candidiasis (thrush)
        - **Non Pharmacologic**
            - Increase fluid intake, add moisture to foods, recommend cold/tepid food temperatures
            - Oral rinses may improve swallowing and taste
            - Ice cubes, sugar free gum and popsicles, frequent sips of cold water, mouth sprays

    - Humidify Supplemental O2 if able
    - To stimulate residual salivary secretion - consume acidic fruits, cucumber, tomatoes, apples (do not consume in mucositis)
  - **Pharmacologic**
    - **Pilocarpine** HCL: 5mg PO tid (titrate up to 10mg tid as needed)
    - Often prescribed as ophthalmic drops 4%, 3 drops PO tid
    - Use <u>after</u> radiation therapy to reduce xerostomia and increase salivary gland function. Effect is temporary and ofshort duration, treatment needs to be life-long; caution regarding cholinergic side effects
- **ORAL INFECTIONS – FUNGAL**
  - Pharmacologic
    - First Line: **Nystatin** suspension (100,000U/ml) swish for 2 minutes then swallow 5ml QID x 7-14days;
    - Second Line: **Fluconazole** 200mg PO x 1 dose; may continue 100mg PO daily x 14days (unclear if necessary)

OROPHARYNGEAL SECRETIONS AT END OF LIFE

- Common at end-of-life
- Not generally a distressing symptom for the patient; moredistressing for those at the bed side – "like snoring"
- There is a lack of evidence supporting the use of anti-secretoryagents for the treatment of secretions, but anti-cholinergic medications are commonly used if large amount of secretions or bothersome
- No single agent has been found to be superior over another
- Agents work by preventing the production of further secretions; they do not dry up secretions already present

DRUG/DOSE	DOSE
Atropine 1% ophthalmic drops (1 drop ~0.5mg)	1-2 drops SL q2h prn
Hyoscine hydrobromide (**Scopolamine**)	0.2mg-0.6mg SC q4h prn
Glycopyrronium (**Glycopyrrolate**)	0.4mg SC q4h prn Note: Does not cross the BBB; consider in patients where sedation is not necessary

Note: Usually started as prn. Can prescribe regularly if secretions are excessive, then reassess once secretions have improved and change from routine to prn if appropriate

SEIZURES

– **ACUTE SEIZURE; Status Epilepticus**
  - Choice of first line agent will depend on medications available and the patient setting
  - Most often in palliative care we use midazolam IM/SC
  - Add phenytoin IV if benzodiazepine ineffective; then consider midazolam continuous infusion or phenobarbital SC if necessary

DRUG / DOSE	FREQUENCY	DURATION OF ACTION
Midazolam (1st line) Dose: 5-10mg IM/SC/IV	q15min	2h
Lorazepam (2nd line) Dose: 2mg SC/IV/IM/SL/PR Max 8mg in 12hrs	q10min	12-24h (IV/SC/SL)
Diazepam (3rd line) Dose: 10-20mg IV q5mins OR PR q30mins	q5min	15-30min
Phenytoin (used in refractory if benzos ineffective, good response in 50% of cases Dose (Loading):15-20mg/kg IV	Q24h	24-48hrs
Phenobarbital Dose: 10-15mg/kg SC/IV/PR		24-48hrs
Midazolam Continuous Infusion (used in refractory cases after 60+ minutes) Dose (Loading): 0.2mg/kg loading dose then 0.2mg/kg/hr infusion SC/IV	Continuous via CADD pump, Syringe Driver, or IV pump)	Continuous

– **ONGOING Anticonvulsant Therapy (Anti-epileptic drugs = AED)**
  - Incidence of seizures is 30% in patients with brain tumors, 20-35% in patients with brain metastases
  - AED started typically only after a seizure, not prophylactically
  - No RCTs to date comparing the superiority of one AED over another; start with monotherapy; use lowest effective dose; check levels where appropriate.
  - Consider drug interactions between chemotherapeutic agents andenzyme-inducing AEDs
  - If seizures recur after starting AED, increase the dose and check for adequate serum drug levels (if appropriate) prior to switching AED or adding a second agent; can call neurology for support

DRUG / DOSE	SIDE EFFECTS	NOTES
Levetiracetam(Keppra®) (PO/IV) - Immediate release: Start at 500mg PO bid - Can increase q2weeks by 500mg/dose Maximum dose 1500mg PO BID	Somnolence, mood disturbance, anxiety,agitation	- Renal dosing required - Few drug interactions and well tolerated (but watch for anxiety and aggression) - Safe with hepatic dysfunction
Carbamazepine (PO/PR) - PR: Rectal suppositories 400mg PR q12h - PO: 400mg/day divided BID (immediate release or extended-release tabs) or QID (oral suspension) - Increase by up to 200mg/day qweekly - Normal maintenance dose 300-1600mg/d Target level 16-48 µmol/L	Serious reactions: TEN, SJS, SIADH, aplastic anemia, agranulocytosis, pancytopenia, pulmonary hypersensitivity, arrhythmias, hepatotoxicity, pancreatitis Common reactions: ataxia, blurred vision, photosensitivity, tremor, muscle twitching, pruritus, xerostomia,HTN	Available as immediate release, sustained release tabs or oral suspension - **Multiple drug interactions!**

Lamotrigine (PO) Weeks 1 & 2: 2.5mg once daily Weeks 3 & 4: 25mg BID Week 5 +: Increase dose by 25-50mg q1-2 weeks until maintenance dose established - Normal maintenance dose 300-500mg/d	Serious reactions: SJS, TEN, serious rash, aseptic meningitis, hepatic failure, suicidality Common Reactions: Diplopia, influenza-like symptoms, poor coordination, tremor, fever, vaginitis, amenorrhea, lymphadenopathy	- May take several weeks to titrate to therapeutic doses. - Risk of rash if titrated too quickly - Discontinue if rash appears - Caution in renal and hepatic failure
Midazolam (SC/IV) Starting: 0.5-1mg SC/IV per hour Titrate upward as necessary	Respiratory depression,sedation	- Requires continuous dosing; usually reserved for end-of-life situations
Phenobarbital (PO/IV/SC/PR) - 1-3mg/kg/day OR 50-100mg BID-TID - Alternatively: 60-200mg PO (liquid) daily OR 50-100mg PO(tablets) BID-TID - Maximum dose 600mg/day	CNS depression, respiratory depression, hepatitis, SJS, erythemamultiforme	- Adjust dose with liver damage and renal failure - Multiple drug interactions including dexamethasone
Phenytoin (PO/IV) - Oral loading dose: 15-20mg/kg PO divided TID given 4h apart, then start maintenance dose 100mg PO TID -Check serum level after 5 days, correcting for albumin -Doses > 300mg/day should be increased by increments of 25-50mg due to hepatic metabolism saturation -Maximum 1200mg / day	Serious reactions: Hypotension and arrhythmias with IV infusions exceeding 50mg/minute, hepatotoxicity, thrombocytopenia, leukopenia, pancytopenia, TEN, SJS, tissue necrosis (IV) Common reactions: Blurred vision, paresthesias, tremor, lymphadenopathy, constipation, gingival hyperplasia	- SR capsules given once daily - Oral suspension available (shake well!) - Oral suspension, immediate release tablets and injectable formulation dosed bid-tid - Multiple drug interactions including dexamethasone

Valproic acid (PO/PR) - Rectal suppositories: 500mg PR q12h - Start at 15mg/kg PO divided BID-TID; increase by 5-10mg/kg/day qweekly until at target serum concentration [200-400µmol/L] - Maximum dose 60mg/kg/day	Hepatotoxicity, thrombocytopenia, abnormal coagulation, bone marrow toxicity with chemotherapy, hair loss, weight gain	- Can start with therapeutic doses immediately - Monitor LFTs, plt, coagulation q3months - Hepatic dosing

DELIRIUM

- ALWAYS determine most likely cause, using bloodwork and imaging as appropriate and treatment of underlying cause(s) only if within patient goals of care
- Symptom management:
  - Antipsychotics are first line treatment
  - Avoid benzodiazepines unless patient has alcohol or benzodiazepine withdrawal or when agitation is not controlled with escalating doses/types of antipsychotics

DRUG / DOSE	FREQUENCY OF TITRATION	NOTES
Haloperidol - Typical **(1st choice)** Starting Doses: -MILD: 0.5-1mg PO/SC q4h prn OR BID - TID -MODERATE: 0.5-2mg (up to 5-10mg) PO/SC/IV q1h prn until calm, then give 50% of the dose needed to calm as maintenance q4-6h Max Dose: 20mg per day	q 1-2 days in increments of 0.5-1mg	- Avoid in Parkinson's disease - Limited anticholinergic effects, less sedating, fewer active metabolites, less hypotensive effects
Risperidone –Atypical Starting Doses: -MILD – MODERATE: 0.5-1mg PO TID Max Dose: 6mg per day	q 2-3 days in increments of0.25-1mg	- Oral only - Lower rates of EPS and faster onset than haloperidol - Fewer anticholinergic side effects than olanzapine
Olanzapine -Atypical Starting Doses: -MILD – MODERATE: 2.5-15mg PO/SC q8h prn OR daily QHS or BID Max Dose: 20mg per day	q2-3 days in increments of 2.5-5mg per dose	- Less effective in hypoactive delirium - Most sedating of the "atypicals" - Lower rates of EPS than haloperidol - Choose if sedation desired - Significant anticholinergic effects possible

Quetiapine –Atypical Starting Doses: -MILD – MODERATE: 6.25-50mg PO BID Max dose: 400mg per day	q 2-3 days in increments of 12.5-50mg per dose	- Use if EPS is a concern (e.g. Parkinson's disease) - Good choice if sedation is required - Lower risk of EPS than with risperidone or olanzapine - Risk of orthostatic hypotension
Methotrimeprazine "Nozinan" Starting Doses: -MILD-MODERATE: 2.5-5mg PO/SC q4h prn -SEVERE: 12.5-50mg SC q4-8h and q1h prn Max dose: 300mg per day	q 2-3 days in increments of 5-10mg per dose	- Drowsiness, sedation, EPS,can lower the seizure threshold, orthostatic hypotension

HYPERCALCEMIA OF MALIGNANCY

- **Definition**: Serum concentration > 2.65 mmol/L
- **Severity**: Low (<3.0), moderate (3.0-3.8), severe (>3.8)
- **Corrected calcium (mmol/L)** = serum calcium + [0.02*(40 –serum albumin)]; however **best to order ionized calcium**
- Malignancies **most** frequently associated with hypercalcemia:
  - Breast cancer, multiple myeloma, NSCLC,ovarian cancer, squamous cell carcinomas
- **Signs & Symptoms (usually seen with calcium > 3.5 mmol/L)**
  - Fatigue, lethargy, weakness, hypotonia
  - Confusion, delirium, cognitive impairment, hallucinations
  - Nausea, vomiting, constipation, anorexia
  - Exacerbation of pain (secondary to bone resorption, bonedeformities, pathological fractures)
  - Pruritus, polyuria, polydipsia, dehydration, renal failure, nephrolithiasis
  - As levels rise: bradycardia, arrhythmias, BBB, AV block, cardiac arrest
- **Treatment – Non-Pharmacologic**
  - Treat the cause (underlying malignancy, if possible)
  - Initiate hydration to Increase the urinary excretion of calcium (recommended for at least 2-3 days); start with 200-250 ml/hour for the first 24h (reduce rate if frail elderly, cardiac history)
  - IV/Subcut Hydration (recommended for at least 2-3 days); normal saline IV 100-120 ml/hr (reduce rate if frail elderly, cardiac history), subcut normal saline 50-75 ml/hr
- **Treatment – Pharmacologic**
  - Stop supplements and drugs promoting hypercalcemia (thiazide diuretics, lithium, ranitidine, cimetidine, Vit A and D)
  - IV Bisphosphonates (if calcium > 3.0 or symptomatic)

- Lower calcium in 48 hrs
- Adverse effects: Renal failure (contraindicated if Cr > 400); caution with nephrotoxic drugs; can cause fever, flu-like symptoms, nausea/vomiting, bone pain, pruritis, osteonecrosis of the jaw

- **Calcitonin (if severe hypercalcemia, > 4.0 mmol/L)**
  - 2-8 units/kg per dose SC q6-12h (max dose 8 units/kg per dose q6h)
  - Use when rapid reduction of serum calcium is required (highly elevated, +++ symptomatic) – reduces serum within 2-6 hrs
  - Administered x2-3 days while awaiting effect of bisphosphonate then discontinue (risk of tachyphylaxis if continued longer)
  - Adverse effects: Nausea, tachyphylaxis
- **Corticosteroid (if bisphosphonate unavailable/ineffective)**
  - Prednisone 40-100mg PO daily for up to 1 week
  - Dexamethasone 4mg PO/SC q6h for 3-5 days

DRUG / DOSE	TIMEFRAME TO EXPECT NORMALIZED CALCIUM LEVELS	EXPECTED DURATION OF EFFECT
Zoledronic Acid - 1st choice 4mg IV over 15 minutes	Within 3-7 days	4-6 weeks
Pamidronate 60-90mg IV over 2-4 hours	Within 3-7 days	3-4 weeks

CATASTROPHIC HEMORRHAGE

- **Definition**: severe bleeding, internal or external, from one or multiple sites, may be life threatening, continuous or intermittent
- **Common Causes:**
  - Cancer or cancer-treatment related:
    - Tumor invasion/destruction/erosion of major vessels, in neck abdomen or chest
    - Thrombocytopenia/marrow failure, coagulopathy
  - Non-cancer related: Variceal bleeding, drugs, coagulopathy
- **Anticipatory Care Plan** (if appropriate based on assessed risk)
  - Order appropriate PRN medications in advance
  - Have equipment (dark towels, suctioning) prepared
  - Communicate possibility of hemorrhage to nursing, family, patient (if appropriate), **ensure clear understanding of Goals of Care**
  - Provide psychological support
- **Management of Bleeding Event**
  - Keep calm and STAY WITH PATIENT (Call for help)
  - Apply pressure to the site if possible, with dark towels
  - Positioning: lateral decubitus with hematemesis, lateral (suspected bleeding side down) for Hemoptysis—prevent choking
  - Administer oxygen, warm blankets for comfort—if tolerated
  - Medication for sedation in the event of catastrophic hemorrhage:
    - **Midazolam – 5-10 mg SC/IV/IM q5-15 minutes prn untiladequate sedation achieved**
    - Opioids for pain management or dyspnea as required
- **Post-Bleed Care**
  - Debrief with patient/family and team, support services

CONTINUOUS PALLIATIVE SEDATION THERAPY

- **Definition**: A process by which medications are used to intentionally lower a patient's level of consciousness to that required to achieve comfort (not necessarily complete loss of consciousness)
- ONLY used when patients are suffering from **refractory symptoms** in the last hours to days of life
    - **Refractory symptoms** are symptoms that remain inadequately controlled after all other appropriate, reasonable and acceptable interventions have failed to provide adequate symptom relief
    - CPST for existential, psychological, social and spiritual distress is controversial. Recommend referral to Palliative Care team, including ethicists, spiritual care, and mental health professionals.
- **Intention**: Provide symptom relief and reduce suffering
- Does not usually alter the timing or mechanism of a patient's death
- NOT a substitute for MAID
- **Palliative consultation** is strongly recommended to determine if symptom is truly refractory, and to ensure reversible causes of distress are ruled out
- **Criteria:**

  1. Death is imminently expected in short days (<14 days)

  2. Symptoms are refractory to all other treatments that are possible, available, and acceptable to the patient within the limited time frame. This has been determined in consultation with a palliative specialist

  3. Informed consent is obtained from the patient or SDM if the patient lacks capacity. This includes that they understand the outcome of the underlying illness is imminent death within hours to days, they understand what to expect during the dying process, and they understand that the goal of CPST is to alleviate refractory suffering and not to hasten death

  4. The goals of care are comfort-focused care. The patient does not wish to have

CPR, intubation, critical care supports, or any interventions to prolong life. This must be documented.

– **Monitor**—continuously on initiation and then q4h by nursing when comfort achieved. Basal rate usual titrated up rather than relying on prn doses.
    - RASS-PAL Scoring system usually used to monitor effect

DRUG	INTIATION DOSE	MAINTENANCE DOSE
Midazolam (Versed) SC/IV **Preferred agent**	1-5mg SC/IV q5min until settled (used in emergencies)	Starting dose: 0.5-1mg/hr and 1-5mgprn Usual effective dose: 1-20mg/hr
	TITRATION	**NOTES**
	Titrate basal rate by 0.5-1 mg q15-30 mg based on symptomatic response to achieve RASS-PAL Score needed to maintain comfort	- In case of breakthrough or symptom crisis, midazolam 2.5-5 mg SC/IV may be given q30 min prn - Consider switching/adding second agent if using > 20mg/hr - Higher doses may be needed in patients with previous benzodiazepine exposure
Lorazepam (Ativan) SC/IV/SL **SECOND LINE**	**INTIATION DOSE**	**MAINTENANCE DOSE**
	0.5-1mg SC/IV q15min OR 1-4mg SL	Starting dose: 1-4mg SC/IV OR 1-8mg SL q2-4hr Usual effective dose:4-40mg/day
	TITRATION	**NOTES**
	Titrate by 0.5-2mg q2h prn	- Peak effect approx 30min after IV dose - Rapid onset - Less rapid titration than Midazolam
Methotrimeprazine SC **SECOND LINE**	**INTIATION DOSE**	**MAINTENANCE DOSE**
	10-25mg q15-30min until settled	12.5-25 SC q4h + 12.5 q1h prn Dose range usually 25-300mg/day
	TITRATION	**NOTES**
	May adjust routine doses q8h until stable	- Useful in delirium - Rapid onset - Long half-life therefore risk of accumulation; may require dose reduction after several days

Phenobarbital SC/IV **THIRD LINE**	**INTIATION DOSE**	**MAINTENANCE DOSE**
	60-120mg SC loading dose	60-120mg q8h regular + 60mg q4h prn <u>Usual dose</u>: 600-1600mg/day <u>Maximum dose</u>: 2500mg/day
	TITRATION	**NOTES**
	Based on symptomatic response to RASS-PAL score needed to maintain comfort	- Rapid onset - Long half-life of 1.5-4.9 days; may need to reducedose after a few days - Abrupt withdrawal after prolonged use could result in seizures

- Benzodiazepines (midazolam and lorazepam) can potentially cause paradoxical agitation (if this occurs d/c the drug and switch to alternate agent)
- Most common initial choice of drug is midazolam; preferred over lorazepam because of faster titration
- Lorazepam via SL route may be the simplest/only option in thehome setting
- For all medications – use the lowest possible dose that achieves an appropriate level of sedation
- "Conscious Sedation" may be possible where the ability to respond to verbal stimuli and communicate is maintained

END-OF-LIFE MEDICATION DEPRESCRIBING AND CONVERSION GUIDE

Dr. A. Agha and Dr. C Goldie (2024)

INTRODUCTION

Patients with life-limiting diseases often remain on medications with little to no short-term benefit in primary or secondary prevention and this can contribute to pill burden, potential adverse drug effects, and has a financial impact. In contrast, in scenarios where patients lose the ability to swallow medications orally, many medications important for symptom management often do not have readily-available parenteral formulations. The inability to administer these medications can exacerbate pre-existing symptoms (e.g. pain, nausea, rigidity) or may result in withdrawal symptoms if abruptly discontinued (e.g. anti-depressants, anti-hypertensives). Non-oral versions of medications of a similar class or for similar indications may exist but may be unfamiliar to prescribers, especially trainees. We hope this guide can help address this gap.

Table 1 outlines clinical signs to monitor for that may indicate a potential impending loss of oral route. This may be pertinent if concerns for medication withdrawal exist, in order to contemplate a taper to avoid sudden discontinuation. Table 2 is the end-of-life medication deprescribing and conversion guide that incorporates pre-existing literature and expert opinion. Medications are categorized by drug classes as per the EphMRA Classification Guideline (i.e. organ systems).

Table 1

SIGNS OF IMPENDING LOSS OF ORAL ROUTE
Palliative Performance Scale (PPS) of 30% or lower
Rapid reduction in PPS
New dysphagia/odynophagia
Underlying morbidity: Head and neck cancer and no alternative enteral route (i.e. g-tube), history of stroke, seizures, dementia, or other cognitive impairments
Presence of aspiration clinical risk factors (pocketing food in the mouth/cheeks, clearing the throat or coughing while eating, drooling, or displaying any difficulty breathing with eating or drinking)
Delirium
Nausea and/or vomiting

Table 2: End-of-life medication deprescribing and conversion guide

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
		CARDIOVASCULAR	
Hyperlipidemia Medications (statins, fibrates, ezetimibe)	Primary or secondary prevention of CV events.	Consider stopping as unlikely to have short term benefits. No tapering required.	No recommended options
Non-Diuretic Antihypertensives (e.g. ACEi, BB, nitro)	Hypertension, secondary prevention of CV events.	Consider stopping unless indication is for angina (e.g. Betablockers, CCB, and nitrates are sometimes used for recurrent angina) or for hypertensive urgency or emergency. Taper gradually and monitor for symptomatic hypertension after discontinuation (chest pain, acute severe back pain, dyspnea, focal neuro symptoms). Beta-blockers in particular should be gradually tapered to avoid tachycardia, hypertension, or ischemia	Nitroglycerin Spray or patch
Diuretics (e.g. Lasix, spironolactone, HCTZ)	CHF, ascites from cirrhosis, anasarca, HTN, secondary prevention for CV events	Consider stopping for mild hypertension or secondary prevention (no tapering required if used for these indications)	Consider Furosemide subcutaneous (single administration should not exceed 20 mg)
Anti-arrhythmics (e.g. amiodarone, procainamide)	Afib, SVT	Consider stopping unless for Symptomatic afib or SVT. Taper gradually and monitor for palpitations, chest pain, dyspnea, etc.	No known non-PO/IV options available
Ivabredine	HFrEF	Would not recommend as may have symptom benefit	No non-PO/IV options available

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
DIABETES / ENDOCRINE			
Insulins	All T1D, T2D with symptoms of metabolic decompensation (polyuria, thirst)	Long-acting insulins -> If T2D, consider stopping if little or no oral intake. If T1D consider decreasing dose but always administering some. Short acting insulins -> Consider stopping or administering only prn if symptomatic (like distressing polyuria, thirst, etc.)	N/A
Oral Agents (e.g. metformin, DPP4i, SGLT2i, GLP-1 agonists)	T2D	Consider if for mild hyperglycemia or secondary prevention of diabetes associated events. No tapering required.	Would not recommend.
Insulin Devices	T1D, T2D	- Continous Glucose Monitoring: Consider removing or setting alarms only during extreme glucose readings - Insulin Pumps: Consider decreasing infusion rate if T1D or stopping in T2D	N/A
Levothyroxine	Hypothyroidism	Do not recommend unless no po route	No recommended options.
GASTROENTEROLOGICAL			
Anti-ulcerants (H2 antagonists, PPI)	GERD treatment or prophylaxis (e.g. high dose steroids or NSAIDs)	Consider if no recent history of GERD, PUD). No tapering required.	H2 Antagonists: Famotidine SC (Conversion factor for PO:SC would be 2:1) PPI: None known. Consider Omeprazole ODT*
Laxatives	Constipation	Would not recommend unless diarrhea.	Enemas or suppositories (glycerin)

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
HEMATOLOGICAL			
Anti-Coagulation Agents (e.g. warfarin, apixaban, LMWH)	Afib, mechanical or bioprosthetic valves, VTE treatment, VTE prophylaxis	Consider stopping if only for VTE prophylaxis and low risk, but will depend on patient preference. No tapering required.	Consider transition of oral agents to LMWH SC depending on indication and risk/time benefits If CKD and on warfarin, consider Fondaparinux or Heparin (however heparin requires IV access for treatment doses)
Platelet Aggregation Inhibitors (e.g. ASA, clopidogrel, ticagrelor)	Primary and secondary prophylaxis (CAD, CVA), DES insertion.	Consider stopping unless DES insertion <3 months ago. No tapering required.	Only available option is ASA suppository.
Vitamin K	Treatment of coagulopathy, warfarin reversal.	Consider stopping. No tapering required.	SC available.
Tranexamic Acid	Hemorrhage (e.g. Hemoptysis)	N/A	Can use injectable solution or crushed tablets topically in case of local bleeding (e.g. mouth sores, cutaneous bleed, nosebleed etc.), or nebulized.

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
Erythropoetin productions	Anemia (e.g. in CKD)	Unlikely short term benefits, consider stopping. No tapering needed.	No recommended options.
INFECTIOUS DISEASES			
Antimicrobials	Infections, infection prophylaxis	Consider stopping antibiotics used for prophylaxis (PJP prophylaxis, COPD prophylaxis) Consider antibiotics if infection causing distressing symptoms and potentially reversible (Pneumonias, SSTI, UTI, herpes/shingles, thrush, etc.)	Ceftriaxone SC, topical (e.g. metronidazole)
HIV Antivirals	HIV+	Recommend consulting with HIV specialists.	No recommended options. Recommend consulting with HIV specialists.
NEUROLOGICAL			
Anti-epileptics	Seizures, neuropathic pain, headaches, psychiatric indications	Would not recommend unless started for seizure prophylaxis and low risk of seizures but always consult with neurology.	Phenobarbital may be administered subcutaneously for seizures. Alternatively can consider subcutaneous benzodiazepines
Levodopa	Parkinson Disease, restless leg syndrome	Recommend continuing as likely has significant symptom benefit. Sudden discontinuation may result in neuroleptic-malignant syndrome.	Duodopa Gel a possibility but would require G/NG-tube; rarely appropriate Apomorphine SC or sublingual film

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
			Rotigotine Transdermal patch Midazolam SC infusion can be considered if significant rigidity after stopping dopaminergic agent
OPHTHALMOLOGICAL			
Anti-Glaucoma Eye Drops (e.g. timolol, bimatoprost)	Glaucoma	Consider stopping if very limited prognosis as prevents worsening of vision only. Can stop without tapering.	N/A
PSYCHIATRIC			
Antipsychotics	Schizophrenia or other psychosis history, nausea, hyperactive delirium	Would not recommend. Consider consulting psychiatry prior to doing so	Several SC options including Haldol and olanzapine
Antidepressants (e.g. SSRI, SNRIs, TCA)	Depression and other psychiatric conditions, neuropathic pain, vasomotor symptoms	Many require tapering to avoid withdrawal. Consider consulting pharmacy or psychiatry. If expect that oral route will be lost soon, recommend tapering pre-emptively.	Escitalopram ODT Mirtazapine ODT If sudden loss of oral route, consider fluoxetine (SSRI) capsule delivered as suppository for several days to reduce risk of withdrawal.
Lithium	Bipolar, MDD	If expect patient to lose oral route, recommend gradually decreasing (over several weeks to months	No available alternative route. Can consider SC

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
		ideally). Consider consulting psychiatry.	antipsychotics to treat active psychosis.
Psychostimulants (e.g. methylphenidate,amphetamines)	ADHD, fatigue in palliative care setting	No special consideration. Can stop without tapering.	No recommended options
Gabanergic agents (e.g. Gabapentin, pregabalin)	Pain (neuropathic), anxiety, seizures, pruritis, hiccups, cough	Would not recommend. If to stop, withdraw gradually >1 week to minimize withdrawal symptoms such as confusion, irritability, tachycardia, diaphoresis) (Norton 2001; Tran 2005)	No known options.
Anti-Alzheimer Products (e.g. donepezil, memantine, rivastigmine)	Alzheimer disease and other dementias.	Consider stopping as unlikely to provide significant symptom benefit in a palliative care setting. Require gradual taper over weeks.	No recommended options
RESPIROLOGY			
Inhaled asthma and COPD medications (e.g. ICS, B2-Agonists, anticholinergic)	COPD, asthma	Would not recommend.	Consider aerochamber, dry-powder inhalers or nebulizers if patient becomes unable to effectively inhale.
ILD Meds (e.g. pirfenidone, nintedanib)	ILD	Consider stopping as unlikely to provide significant symptoms benefit. No tapering required.	No recommended options
Pulmonary Arterial Hypertension meds (e.g. PDE5 inhibitors, prostacyclin pathway	pulmonary arterial hypertension	Recommend consulting with appropriate specialists	SC formulations available for some agents. Consult with appropriate specialists.

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
agonists, endothelin receptor antagonists)			
RHEUMATOLOGIC / MSK			
Immunosuppressants (e.g. anti-TNF, interleukin inhibitors, tacrolimus, mycophenolate mofetil)	Transplant recipient, autoimmune diseases (rheumatoid arthritis, IBD, psoriasis)	Always consider consult with appropriate transplant team for transplant recipients.	Consult with transplant team if pertinent
Allopurinol	Gout flare prevention, TLS prophylaxis	Consider unless frequent gout flares. No tapering required.	No known options
Bisphosphonates	Osteoporosis. Hypercalcemia of malignancy	Consider stopping unless for symptomatic hypercalcemia from bony mets. No tapering required.	No known options
NSAIDs	Pain, migraines, fever, gout	Consider stopping if patient has feels has not obtained significant benefit. No tapering required.	Consider Ketorolac SC for symptomatic fever. Alternatively consider SC steroids for anti-inflammatory effects.
UROLOGIC			
Prostate meds (e.g. tamsulosin, dutasteride, finasteride)	BPH	Do not recommend deprescribing unless foley in place	Limited options, consider insertion of Foley or regular bladder scans and I/O cath if required
Meds for Urinary Incontinence (e.g. oxybutynin)	Overactive bladder	Consider stopping if patient has feels has not obtained significant benefit. No tapering required.	No recommended options
OTHER			

MEDICATIONS	INDICATIONS	DEPRESCRIBING CONSIDERATIONS	COMFORT-FOCUSED OPTIONS
Vitamins and Supplements and Minerals	Primary or secondary prevention, low plasma concentrations	Consider stopping unless known low plasma levels. No tapering required.	No recommended options
Cannabinoids (e.g. nabilone)	Nausea and vomiting associated with chemo, pain, anxiety	Consider stopping if patient has feels has not obtained significant benefit. Recommend slow taper if long term user.	Alternative options include sublingual oil or sprays. Do not recommend vaporizing.
Nicotine including tobacco products	Prevention of nicotine withdrawal	Administer to prevent withdrawal in hospitalized patients or if patients no longer able to smoke	Transdermal patch, inhalation
Alcohol	N/A	Administer benzodiazapines as per CIWA protocol	Subcutaneous lorazepam or diazepam