Guidelines for Weaning and Incorporation of Enterally Administered Medications for Management of SEDATION in Mechanically Ventilated Patients with COVID-19 (TABLE 1)

If RASS Goal 0 to -3

Wean sedative infusion as tolerated (wean sedative first before weaning opioid infusion)

If weaning sedative infusion leads to agitation, choose from one of the following options based on current sedative/duration:

OPTION 1: > 7 days of continuous infusion benzodiazepines

Consider enteral chlordiazepoxide or lorazepam. Attempt to wean infusion after 1-2 hours (see TABLE 2 for initial dosing)

Increase by 50-100 mg per dose (chlordiazepoxide) or 2-4 mg (lorazepam) while maintaining Q 6-8 h frequency every 12-24 h (Taper these agents by 20% per day as tolerated [increasing frequency first])

If rapidly escalating doses of chlordiazepoxide or lorazepam and no bradycardia, add adjunct dexmedetomidine. Start at 0.2 mcg/kg/h and follow titration orders to goal RASS within Epic/Allscripts to max 1.5 mcg/kg/h. Wean benzodiazepine after 1-2 h.

OPTION 2: < 7 days of continuous infusion benzodiazepines

[Preferred] Begin dexmedetomidine if no bradycardia

- Start at 0.2 mcg/kg/h and follow titration orders within Epic/Allscripts order to max 1.5 mcg/kg/h. Wean benzodiazepine after 1-2 h.

Consider standing chlordiazepoxide or lorazepam (see TABLE 2 for initial dosing) If unable to start dexmedetomidine

OPTION 3: Only propofol

[Preferred] Begin dexmedetomidine if no bradycardia

- Start at 0.2 mcg/kg/h and follow titration orders within Epic/Allscripts order to max 1.5 mcg/kg/h

Consider enteral chlordiazepoxide or lorazepam (see TABLE 2 for initial dosing) if unable to start dexmedetomidine

If unable to start chlordiazepoxide due to inability to use enterally administered medications, consider standing IV lorazepam (1-2 mg IV Q 6 h, increase by 0.5 -1 mg per dose while maintaining Q 6 h frequency every 12-24 h) or IV phenobarbital (65 mg IV Q 12 h, increase by 65 mg per dose every 24 h to max 400 mg/day)

If continuous infusion benzodiazepine is weaned to off and ***ventilatory dyssynchrony leading to occasional desaturation:***

- Bolus dose of opioid (bolus from continuous IV opioid) *[preferred]* OR midazolam 2 mg IV x1 PRN (if no continuous IV opioid present or ventilator dyssynchrony unable to be treated with opioid)

If continuous infusion benzodiazepine is weaned to off and ***frequent ventilatory dyssynchrony and desaturation occurs:***

- Bolus opioid for dyssynchrony and increase opioid infusion dose *[preferred]* OR start propofol if not already on *[second line option]* OR start midazolam bolus doses or infusion after bolus *[third line option]*

If ***hyperactive delirium*** is suspected

Consider enteral quetiapine 50-100 mg Q 6-8 h, increase by 50 mg per dose Q 12-24 h *[preferred]*; olanzapine 5-10 mg Q 24 h, increase by 5-10 mg per dose *[2nd line option]*

- If unable to start quetiapine or olanzapine due to inability to use enterally administered medications or side effects consider valproic acid 250-500 mg IV q 6-8 h, increase by 250 mg per dose Q 12-24 h to max 23 mg/kg/day *[preferred]*
- Consider haloperidol 2-5 mg IV q 6 h if unable to use valproic acid due to side effects or drug interaction with

If RASS Goal -4 to -5, FiO_2 < 80% and NOT RECEIVING chemical paralysis

- Consider enteral chlordiazepoxide or lorazepam via feeding tube to decrease IV sedative consumption if receiving >7 days of continuous infusion benzodiazepine (see TABLE 2 for initial dosing). Attempt weaning infusion in 1-2 h.

If RASS Goal -5, FiO_2 > 80% and RECEIVING chemical paralysis

- Continue continuous IV midazolam or propofol. Follow steps above when chemical paralysis discontinued

V. 4/5/20

Guidelines for Weaning and Incorporation of Enterally Administered Medications for Management of PAIN in Mechanically Ventilated Patients with COVID-19 (TABLE 3)

If RASS Goal 0 to -3

Attempt IV opioid wean to OFF

- Every patient will have different pain control needs (suctioning, turning, previous opioid use, etc); however, for the most part intubated patients with COVID-19 will not have surgical pain and opioids will be used to maintain ventilator synchrony to maximize lung protective ventilation

If there are ongoing pain needs with weaning of continuous IV opioids, consider the following:

- Initiate oral opioid via feeding tube if unable to wean continuous IV opioid in 24-48 h **(see TABLE 4 below)** - decrease dose by 20% per day as tolerated once continuous IV opioid discontinued
- Optimize non-opioid therapy if ongoing pain (e.g., Critical Care Pain Observation tool >3 or Numerical rating Scale >3; may use one or all of the listed below options in no particular order)

Acetaminophen tablets
650 mg Q 6 h

- Dose reduce (max 2 g per day) in patients with liver injury
- Crush for administration

Gabapentin tablets/capsules
200-300 mg Q 8 h

- Increase dose daily by 100-200 mg per dose to max dose of 800 mg enterally Q 8 h
- Dose adjust for renal dysfunction **(see TABLE 5 below)**
- Notable adverse effect: sedation
- Strategies for weaning/ discontinuation:
  - Discontinue all doses if patient obtunded
  - Reduce dose by 25-50% per day (decrease dose, maintain frequency when possible)

Ketamine infusion
3-5 mcg/kg/min

- Avoid in patients with heart failure
- Notable adverse effects (uncommon with this dose): hypertension, tachycardia, delirium, nystagmus, increased respiratory secretions

Lidocaine patch applied to site of pain
(E.g., chest tube, back pain, etc)

- Caution in patients who are febrile or receiving vasopressors (variable absorption)

If RASS Goal -4 to -5 (NON-Paralyzed Patients)

- Initiate enteral opioid to decrease IV opioid consumption when appropriate within 24-48 hours post intubation **(see TABLE 4 below)**

If RASS Goal -5 (Paralyzed Patients)

- Continue continuous IV opioids

Supplementary Tables

TABLE 1

Drug	Route	Dose equivalency (mg)*	Products available on formulary	Recommended frequency	Active metabolites	Comments
Chlordiazepoxide	PO	50	5 mg, 10 mg, 25 mg	Q 6-8 h	Y	• In the first 36-46 hours there is a short half-life; however, as active metabolites accumulate the half-life becomes prolonged
Diazepam	IV	5	(variable)	Q 4-6 h	Y	• Preferred if alcohol withdrawal suspected • Quick onset and prolonged duration of action • Tablets can be crushed for administration via feeding tube • Active metabolites accumulate with renal dysfunction
Diazepam	PO	10	2 mg, 5 mg, 10 mg	Q 6-8 h		
Lorazepam	IV	1	(variable)	Continuous infusion Q 6-8 h	N	• Preferred if renal or hepatic dysfunction • IV: Increased risk for propylene glycol (PG) toxicity with doses > 3 mg/h (lower doses if renal impairment and no dialysis) • To evaluate for PG accumulation, assess for increased anion gap (>10) and increased osmolar gap (> 10 mOsm/L)
Lorazepam	PO	1	0.5 mg, 1 mg, 2 mg	Q 6-8 h	N	
Midazolam	IV	2	(variable)	Continuous infusion Q 6-8 h	Y	• Metabolite may accumulate in renal dysfunction
Propofol	IV	--	(variable)	Continuous infusion	N	• Propofol infusion syndrome possible with use >7 days or >60 mcg/kg/min > 48 h (can rarely happen in a shorter time and at lower doses) • Bradycardia/hypotension possible • Monitor CPK and TG every 72-96 hours
Dexmedetomidine	IV	--	(variable)	Continuous infusion	N	• Bradycardia/hypotension possible • Should not be used for patients requiring RASS goal of -4 or -5 (e.g.; for RASS -5 required prior to paralytic initiation)
Haloperidol	IV/PO	--	0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg	Q 6-8 h	N	• IV peaks in 30 min • IV associated with increased risk for QTc prolongation • Avoid in patients with baseline or risk factors for QTc prolongation • Monitor QTc q2x/week, can decrease QTc monitoring to weekly if no other risk factors for prolongation • Tablets can be crushed for administration via feeding tube
Olanzapine	PO/SL	--	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg	Q 12-24 h	N	• Time to peak 6 hours • Can cause QTc prolongation, avoid in patients with baseline or risk factors for QTc prolongation • Monitor QTc q2x/week, can decrease QTc monitoring to weekly if no other risk factors for prolongation • Tablets can be crushed for administration via feeding tube • Maximum dose 20 mg/day
Quetiapine	PO	--	12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg	Q 6-12 h	N	• Time to peak 90 min • Maximum dose 800 mg/day (maximum studied for delirium 400 mg/day) • Tablets can be crushed for administration via feeding tube • Extended release tablets cannot be crushed, swallowed whole • Can cause QTc prolongation, avoid in patients with baseline or risk factors for QTc prolongation • Monitor QTc q2x/week, can decrease QTc monitoring to weekly if no other risk factors for prolongation

Valproic acid	IV/PO	--	(variable)	Q 6-8 h	N	• Time to peak ~4 h • Can cause hepatotoxicity, thrombocytopenia, leukopenia, pancreatitis, hyperammonemia • Monitor liver function (AST/ALT, alkaline phosphatase, bilirubin), CBC, amylase, lipase, ammonia 2x/week • Do NOT use with carbapenem antibiotics; valproic acid will decrease serum concentration of carbapenem antibiotics • Serum levels do not correlate with efficacy when used for management of hyperactive delirium; avoid elevated levels to decrease risk for side effects • Immediate release tablets can be crushed for administration via feeding tube • Extended release, delayed release tablets cannot be crushed, they should be swallowed whole

TABLE 2

Current regimen	Suggested initial dose (may increase daily)*	
Midazolam $\leq$ 2 mg/hr Propofol < 40 mcg/kg/min	Chlordiazepoxide 50 mg Q 6-8 h	Lorazepam 1 mg Q 6-8 h
Midazolam 2-5 mg/hr Propofol 40-60 mcg/kg/min	Chlordiazepoxide 50-100 mg Q 6-8 h	Lorazepam 1-2 mg Q 6-8 h
Midazolam >5 mg/hr Propofol > 60 mcg/kg/min	Chlordiazepoxide 150-200 mg Q 6-8 h	Lorazepam 3-4 mg Q 6-8 h

TABLE 3

Drug	Route	Dose equivalency (mg)*	Products available on formulary	Recommended frequency	Active metabolites	Comments
Fentanyl	IV	0.02	(variable)	Continuous infusion	N	

Fentanyl patch	Topical	--	12 mcg/h
			25 mcg/h
			50 mcg/h
			75 mcg/h
			100 mcg/h
				Q 72 h (preferred), Q48 h	N	• Use with caution as pharmacokinetics often altered in critically ill patients
						  • Increased absorption with fever or application to broken skin
						  • Decreased absorption with high vasopressor doses, hypothermia, peripheral edema
						• Difficult to titrate due to prolonged pharmacokinetics
						• Onset of action: 12-24 h; Offset of action after removal: 72-96 h
						• Do not cut patches
						• Decrease infusion by up to 50% six hours after placement of the first patch. Titrate down further twelve hours after application of the first patch

Hydromorphone	IV	0.3	(variable)	Continuous infusion / Q 3-6 h PRN to pain scale or round the clock	N	
Hydromorphone	PO	1.5	2 mg, 4 mg, 8 mg	Q 4-8 h Q 3-6 h PRN to pain scale or round the clock	N	• Order immediate release tablets and crush for administration via feeding tube • Extended release tablets cannot be crushed, they should be swallowed whole

Morphine	IV	2	(variable)	Continuous infusion / Q 3-6 h PRN to pain scale or round the clock	Y	• Hypotension related to histamine release may occur • Active metabolite can accumulate and lower seizure threshold in patients with renal impairment • Order immediate release tablets and crush for administration via feeding tube • Extended release tablets cannot be crushed, they should be swallowed whole
Morphine	PO	6	15 mg, 30 mg	Q 3-6 h PRN to pain scale or round the clock	Y	
Oxycodone	PO	4	5 mg, 10 mg, 15 mg	Q 4-6 h PRN to pain scale or round the clock	N	• Avoid combination product acetaminophen/oxycodone. Prescribe acetaminophen separately, if needed • Order immediate release tablets and crush for administration via feeding tube • Extended release tablets cannot be crushed, they should be swallowed whole
Methadone	IV	--	10 mg	Q 8-12 h	Y	• Unique pharmacokinetics of methadone makes determining dosing equivalence difficult • Can cause QTc prolongation • Avoid in patients with baseline or risk factors for QTc prolongation (e.g.; concomitant hydroxychloroquine, azithromycin) • Monitor QTc q2x/week, can decrease QTc monitoring to weekly if no other risk factors for prolongation or increase monitoring in patients with risk factors • 1 mg IV methadone = 2 mg PO methadone
Methadone	PO	--	5 mg, 10 mg	Q 8-12 h		
Remifentanil	IV	0.02	(variable)	Continuous infusion	N	--
Sufentanil	IV	0.002	(variable)	Continuous infusion	N	--

This is only for first dose and does NOT take into account active metabolites that may accumulate

TABLE 4

Current regimen	Suggested initial dose (may increase daily)*
Fentanyl ≤ 75 mcg/h OR Hydromorphone ≤ 1.2 mg/h	• Hydromorphone 2-4 mg Q 6-8h OR • Oxycodone 10-20 mg Q 6-8h
Fentanyl 100-200 mcg/h OR Hydromorphone 1.4-2.5 mg/h	• Hydromorphone 8-16 mg Q 6-8h (preferred) OR • Oxycodone 20-30 mg Q 6-8h
Fentanyl >200 mcg/h Hydromorphone >2.5 mg/h	• Hydromorphone 32 mg Q 6-8h

use tablets; crush to administer via feeding tube

*decrease infusion as allowable after initiation of standing opioid feeding tube

TABLE 5 – Renal dose adjustments for gabapentin

Tablet/capsule size available*	Estimated creatinine clearance (mL/min)	Approximate dose adjustment
100 mg, 300 mg, 400 mg, 600 mg, 800 mg *tablets can be crushed and capsules may be opened and contents given via feeding tube	>79	None
	50-79	None
	30-49	50% reduction (reduce dose, maintain Q 8h frequency)
	15-29	75% reduction (reduce dose and decrease frequency to Q 12h)
	< 15	90% reduction (reduce dose and decrease frequency to Q 24)
	iHD	Max dose 300 mg Q nightly (give at 21:00 to prevent pulling of drug from iHD sessions)
	CRRT	Max dose 600 mg/day