Weaning of Analgesia & Sedation and Management of Iatrogenic Withdrawal Syndrome

Joel Lim

Introduction

The care of the critically ill child usually involves analgesia and sedation to facilitate optimal mechanical ventilation, safe diagnostic and therapeutic procedures, ensure comfort and minimize distress.

Common agents used include opioids (e.g. morphine, fentanyl) and benzodiazepines (e.g. midazolam, lorazepam and diazepam). Other agents include dexmedetomidine, clonidine, ketamine, chloral hydrate, propofol, antipsychotics and barbiturates.

The ideal use of analgesia and sedation involves striking a balance between adequate pain control and sedation to facilitate care within the trajectory of critical illness, and performing timely, safe and controlled weaning of such medications while avoiding the development of iatrogenic withdrawal syndrome. Before weaning, analgesia/sedation are titrated based on targeted pain and state behaviour assessment (SBS) scores.

Over-sedation should also be avoided, as it can increase the duration of mechanical ventilation, intensive care unit (ICU)/hospital length of stay and increase the risks of iatrogenic withdrawal syndrome, delirium, ICU-related muscle weakness and contribute to prolonged immobility with its associated complications, such as the post-intensive care syndrome.

Contrary to common perception, opioids and benzodiazepines increase sleep disruption and reduce restorative sleep. Thus, a sedated patient is not necessarily a well-rested patient. Just as a ventilator strategy depends on a patient's trajectory, **a sedation strategy should also follow the patient's trajectory and weaning analgesia and sedation should begin as soon as it is safe and appropriate to do so**.

Not all efforts to achieve comfort require a prescription. Non-pharmacological measures should be instituted at all times to calm patients. These may facilitate a dose-reduction in analgesics and sedation, with the associated benefits of improved awakening, better breathing effort and better sleep.

Non-Pharmacological measures include:

1. Reducing environmental stimuli such as light and noise (especially at night)
2. Promotion of sleep and maintaining a day-night routine
3. Optimising patient position
4. Swaddling infants or using weighted blankets
5. Comforting touch / massage / rocking
6. Parental involvement in care
7. Regular feeds for infants
8. Ensuring adequate hydration
9. Music / Play / Relaxation / Distraction therapy

Identification of Iatrogenic Withdrawal Syndrome

Definition:
Iatrogenic withdrawal syndrome is the term used for a characteristic pattern of unpleasant signs and symptoms that typically follows too rapid tapering or abrupt cessation of opioid, benzodiazepines or other drugs with central nervous system depressant effects.

- All commonly used opioids, benzodiazepines and medications including dexmedetomidine, clonidine, chloral hydrate, ketamine and barbiturates are associated with withdrawal.
- Withdrawal effects may occur in children who have received opioids or benzodiazepines for as few as 3 days.
- Symptoms of withdrawal may take up to 48 – 72 hours to manifest.
- It is difficult to distinguish between signs of opioid and benzodiazepine withdrawal.

Signs and Symptoms of Withdrawal

CNS Irritability	GI Disturbances	Autonomic Dysfunction
Irritability	Diarrhoea	Fever
Poor sleep pattern	Vomiting	Tachypnoea
Hallucinations	Abdominal pain	Tachycardia
Tremors	Gagging	Hypertension
Dilated pupils	Uncoordinated suck/swallow	Increased secretions/sweating
Muscle spasms/aches		Yawning/hiccups
Seizures		Goosebumps/chills

Risk Factors for Withdrawal

1. Infants less than 6 months of age
2. Pre-existing cognitive impairment
3. Use of opioids / benzodiazepine / α_2-adrenergic agonists for 5 days or more
4. Use of > 2 agents or high doses (e.g. morphine > 40 mcg/kg/hr, midazolam > 4 mcg/kg/min)
5. Potent short-acting opiates (fentanyl) may be associated with tolerance within 48 - 72 hours
6. Patients with previous experience of withdrawal

Withdrawal Assessment Tool (WAT-1) Scoring

The first step in withdrawal management is to perform a withdrawal assessment. We use the WAT-1 score in our institution. However, **the diagnosis of withdrawal is one of exclusion**.

Steps to use the WAT-1 score:

- **Start WAT-1 scoring when the decision is made for weaning**, with a baseline score obtained before weaning is initiated.
- WAT-1 scoring should be performed at least Q8H, but can be more frequent if required.
- Scoring should be continued until 72 hours after the last opioid/benzodiazepine/adjunct drug is served.

Interpretation of the WAT-1 score:

- A higher WAT-1 score indicates more withdrawal symptoms.
- WAT-1 scores should be interpreted based on their trend over time
- When interpreting WAT-1 scores, consider the patients baseline neurodevelopmental status, course of illness and other potential environmental contributing factors.
- New pathologies can cause symptoms/signs that can be mistaken for withdrawal.
- An intervention is recommended if the **WAT-1 score is ≥3 or >2 above baseline.**

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier														
	Date:													
	Time:													
Information from patient record, previous 12 hours														
Any loose/watery stools	No = 0 Yes = 1													
Any vomiting, retching, gagging	No = 0 Yes = 1													
Temperature > 37.8 °C	No = 0 Yes = 1													
2 minute pre-stimulus observation														
State	SBS[1] ≤ 0 or asleep/awake calm = 0 SBS[1] ≥ +1 or awake distressed = 1													
Tremor	None/mild = 0 Moderate/severe = 1													
Any sweating	No = 0 Yes = 1													
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1													
Yawning or sneezing	None or 1 = 0 >2 = 1													
1 minute stimulus observation														
Startle to touch	None/mild = 0 Moderate/severe = 1													
Muscle tone	Normal = 0 Increased = 1													
Post-stimulus recovery														
Time to gain calm state (SBS[1] ≤ 0)	< 2 minutes = 0 2 - 5 minutes = 1 > 5 minutes = 2													
Total Score (0-12)														

3 indicators obtained from the **preceding 12 hours** are scored with one point:

- **Loose/watery stools** which are not consistent with the patients' baseline.
- **Vomiting/retching/gagging** which cannot be attributed to other causes/interventions.
- **Temperature ≥ 37.8°C** that is relatively sustained and not associated with infection.

5 indicators assessed during a **2-minute observation before stimulating** the patient are scored with one point:

- **State behaviour** based on observation (asleep/awake/calm=0 or awake/distressed=1).
- **Tremors** that are moderate/severe and cannot be attributed to another cause.
- **Sweating** that is not related to appropriate temperature regulation response.
- **Uncoordinated/repetitive movements** that are moderate to severe such as head turning, torso arching or limb flailing.
- **Yawning/sneezing** that is observed more than once in the 2-minute observation period.

2 indicators assessed **during a progressive stimulus*** are scored with one point:

- **Startle to touch** that is moderate to severe.
- **Muscle tone** that is increased.

*A progressive stimulus is used to elicit the patients' response. Escalate to the next step if there is no response: Calling patients' name calmly → calling patients' name + gentle touch → noxious stimuli such as endotracheal suctioning or applying pressure to the nail bed.

1 indicator assessed during an **observation period after the stimulus** is scored with up to two points:

- Time to gain calm state: Score 2 points if returning to calm takes > 5 minutes. Score 1 point if returning to calm takes 2 – 5 minutes.

Generally, a WAT-1 score of ≥3 or >2 above baseline is suggestive of withdrawal.

Weaning of Analgesia & Sedation and Treatment of Iatrogenic Withdrawal Syndrome

Titration ≠ Weaning → Our sedation protocol allows nurse-led titration of sedation up/down based on SBS scores. Note that down-titration is not the same as weaning.

A sedation strategy should follow the trajectory of the patients' illness. As critical illness evolves over time, sedation targets should be reassessed daily and the decision to begin weaning should be made as early as it is safe to do so. This algorithm serves as a guide for weaning sedation, however, in the event of clinical deterioration, consider "exiting" the patient from the algorithm, with sedation targets reassessed and sedatives managed at the discretion of the ICU team.

Inclusion Criteria:

1. Any neonate with postnatal exposure to opioids or benzodiazepines for 5 days or more
2. Any infant or child with exposure to opioids or benzodiazepines for 5 days or more

Exclusion Criteria:

1. Neonates with antenatal exposure to opioids or benzodiazepines / neonatal abstinence syndrome (which uses the Lipsitz or Finnegan score for assessment)
2. Any patient currently receiving neuromuscular blocking agents
3. Any patient being co-managed with The Children's Pain Service
4. Consider "exiting" the algorithm if the patient turns unwell

High Risk Groups which require extra caution during weaning:

1. Patients at high risk of pulmonary hypertension
2. Patients undergoing neuroprotection (e.g. refractory intracranial hypertension)
3. Patients on ECMO / CRRT support
4. Refractory seizures requiring high dose anti-epileptic medication
5. Immediate post-operative tracheostomy

The following questions are meant to aid decision making when developing and executing a weaning plan. They form an **Approach to weaning of analgesic/sedative medications**:

1. Is weaning now appropriate in the context of this child's illness?
2. Any active pain sources? (consider weaning sedatives before analgesia)
3. Are there any reasons to delay weaning? (Planned procedures / imaging such as MRI)
4. What medications has the child received (duration, dose, number of agents)?
5. Are there any risk factors for iatrogenic withdrawal syndrome?
6. Are there signs that the rate of weaning should be slowed? Or hastened?
7. Have enteral feeds been established?
8. Are adjunctive medications necessary?

General steps for Weaning

- Assessment of patient and sedation targets → Decision to wean → Start WAT-1 scoring Q8H (Document: Date/Time for the start of weaning in doctors plans)
- Take note of all regular and PRN analgesic/sedative medications → Decide on order of wean
    - The first drug to wean depends on the clinical situation
    - If there is an ongoing analgesic requirement → Optimize non-opioid analgesics and consider weaning benzodiazepines first
    - If also on dexmedetomidine or clonidine, weaning of all agents can be performed concurrently, but should occur at staggered timings
- Risk factors for withdrawal? → Consider a slower weaning rate
- Regular patient assessment → Consider more frequent WAT-1 scores if necessary
- Tolerating full enteral feeds? → Consider conversion to enteral formulation

Weaning Guidelines for IV Analgesia and Sedation Infusions

GOAL: To reduce exposure to sedatives and minimize risk of iatrogenic withdrawal

READY TO WEAN?
Any active pain?
Any reason to delay weaning?

→ Order pre-wean WAT-1 Q8H for moderate/high risk groups

→ **WEAN ACCORDING TO WITHDRAWAL RISK**

Other Risk Factors for Withdrawal
- Age < 6 months
- Pre-existing cognitive impairment
- Use of high doses / multiple agents
- Previous withdrawal

Principles for Weaning:
- Ensure non-pharmacological measures in place
- Consider risk factors for withdrawal
- Order of drug wean according to clinical situation
- **If on multiple agents, stagger weaning times for different drug classes***

LOW RISK
(**<5 days** of continuous exposure)
- Gradual tapering not required
- Assess WAT-1 only if clinical concerns present

MODERATE RISK
(**5-10 days** of continuous exposure, or shorter if withdrawal is suspected)
- **Wean IV infusion rate by 20% of original pre-wean dose Q24H**
- If other risk factors present → Consider 10% wean Q24H
- If full enteral feeds tolerated → Consider enteral conversion

HIGH RISK
(**>10 days** of continuous exposure, or shorter if withdrawal is suspected)
- **Wean IV infusion rate by 10% of original pre-wean dose Q24H**
- If other risk factors present → Consider 5% wean Q24H or 10% wean Q48H
- If full enteral feeds tolerated → Consider enteral conversion

Assess for Withdrawal: WAT-1 score Q8H (Or more frequent if necessary)

CLINICAL DETERIORATION?
Consider "Exiting" the Algorithm

Weaning successful
WAT-1 < 3 AND < 2 above baseline

→ **Continue weaning:**
If WAT-1 persistently ≤ 1, consider accelerating wean

Monitor WAT-1 score until 72H after last dose of sedatives

Withdrawal suspected
- WAT-1 ≥ 3 AND > 2 above baseline
- For dexmedetomidine: Rebound ↑HR or ↑BP
- Consider differentials for ↑WAT-1 score

→ **Serve Rescue Dose (Purge from pump)**
- Morphine: IV 0.05mg/kg (50mcg/kg or 2.5ml†)
- Midazolam: IV 0.06mg/kg (60mcg/kg or 1ml†)

(Serve either drug or both, depending on clinical suspicion or last weaned drug)
Hold weaning for 24H
Repeat WAT-1 score in 1H after rescue doses!

WAT-1 < 3
- Continue current regular dosing
- Continue weaning after 24H

WAT-1 ≥ 3
- Consider differentials for ↑WAT-1 score
- Repeat rescue dose
- If ≥ 3 rescue doses given, ↑ last weaned drug to previous dose
- Resume wean after 24H, KIV reduce rate of wean
- Consider adjuncts. E.g. IV / PO Clonidine 1-2 mcg/kg Q4-8H

Differentials for Agitation or ↑WAT-1 score
- Pain
- Hypoxia / Hypercarbia
- Ventilator dyssynchrony
- Sepsis
- Low cardiac output state
- Hypoglycemia
- Feed intolerance
- Itch / Full bladder / Constipation
- Delirium
- Disrupted sleep

*E.g. If weaning Morphine/Midazolam by 10% Q24H → Wean Morphine at 0800hrs and Midazolam at 2000hrs

†Rescue dose volumes based on standard morphine/midazolam dilution

Rescue/Prophylactic Doses

Rescue Drug	Dosage	Rescue Drug	Dosage
IV Morphine	0.05 mg/kg (50mcg/kg)	PO Morphine	0.15 mg/kg
IV Midazolam	0.06 mg/kg (60mcg/kg)	PO Lorazepam	0.05 mg/kg

- Use similar doses for both "rescue" or "prophylactic" doses before handling a patient.
- All rescue/prophylactic doses served (per drug class) will be counted when assessing response to weaning.
- If 3 or more rescue/prophylactic doses (per drug class) are required, consider increasing basal infusion rate/enteral dose of that specific drug to the previous dose.
- Administered rescue/prophylactic doses are to be documented within the flowsheets.

Intravenous to Enteral conversion of Opioids, Benzodiazepines and α_2-adrenergic agonists

- As soon as <u>full enteral feeds</u> are tolerated and significant periods of nil by mouth are not anticipated, all intravenous medications should be converted to enteral formulation.
- Use the conversion formulae provided to facilitate conversion from IV to enteral formulations. Please **<u>stagger</u>** the timing for conversion if converting 2 or more agents.
- For IV Dexmedetomidine, consider converting to PO Clonidine only when at infusion rates of 0.5 mcg/kg/hr or less.

IV to IV/Enteral Formulation Conversion Table*		
Original Agent	**Desired Agent**	**Formula**
IV Morphine	PO Morphine	__mg/24hr IV Morphine x 3 = __mg/24hr PO Morphine (divide into Q4-6H dosing)
IV Fentanyl	IV Morphine	__mcg/kg/hr IV Fentanyl x 25 = __mcg/kg/hr IV Morphine
IV Fentanyl	PO Morphine	__mcg/24hr IV Fentanyl x 0.1 = __mg/24hr PO Morphine (divide into Q4-6H dosing)
IV Midazolam	PO Lorazepam	__mg/24hr IV Midazolam x 0.1 = __mg/24hr PO Lorazepam (divide into Q6H dosing)
IV Dexmedetomidine (Convert when ≤0.5mcg/kg/hr)	PO Clonidine	• If IV Dexmedetomidine is running at 0.2-0.3 mcg/kg/hr → Convert to PO Clonidine 2 mcg/kg/dose Q6H • If IV Dexmedetomidine is running at 0.4-0.5 mcg/kg/hr → Convert to PO Clonidine 3-5 mcg/kg/dose Q6H

***Use conversion calculator at Annex A**

Steps in Converting from IV to Enteral formulation	
IV to PO Opioid/Benzodiazepine or IV Dexmedetomidine to PO Clonidine	
Step 1	Start PO Morphine / Lorazepam / Clonidine at calculated dose
Step 2	Wean IV Opioid / Midazolam / Dexmedetomidine infusion by 50% 30 minutes after the **2nd** PO Opioid / Midazolam / Clonidine dose
Step 3	Turn off IV Opioid / Midazolam / Dexmedetomidine infusion 30 minutes after the **3rd** PO Opioid / Midazolam / Clonidine dose

Weaning Enteral Opioids, Benzodiazepines and Clonidine

- Once enteral analgesia and sedation has been established for at least 24 hours, the same rate of weaning for IV medications can be followed (e.g. wean total daily dose by 10-20% Q24-48H as in weaning guideline).
- For PO Clonidine, wean by reducing by 1 mcg/kg/dose every 24 hours until dose reaches 1 mcg/kg/dose.
- At the approximate minimum enteral dose, further weaning involves keeping the same dose, but increasing the dosing interval (e.g. Q4H → Q6H → Q8H → Q12H → Q24H → Off).
- The dosing interval should be increased Q24H (e.g Q4H for 24hrs → Q6H for 24hrs, etc) (or over the same period of weaning previously. e.g. if steps in weaning were carried out every 48 hours, then increase the dosing interval every 48 hours).

Agent	Minimum Enteral Dose	Maximum Enteral Dose
PO Morphine	0.1mg/kg/dose	15 mg/dose
PO Lorazepam	0.02mg/kg/dose	2 mg/dose
PO Clonidine	1mcg/kg/dose	5 mcg/kg/dose (100 mcg/dose)

- If experiencing difficulties weaning opioids or benzodiazepines, or if attempting to promote spontaneous breathing, consider slowing the wean of α_2-adrenergic agonists and focus on weaning opioids/benzodiazepines first.

- In the event of increasing WAT-1 scores or concerns of withdrawal, take the following steps (as in the weaning guideline):
  - Consider differentials for the increase in WAT-1 score
  - Serve a rescue dose and repeat WAT-1 score in 1 hour (choice of rescue drug depends on clinical suspicion or last weaned drug)
  - Hold weaning and keep current regular dose for 24 hours
  - If ≥3 rescue doses given, increase last weaned drug to previous dose
  - Resume wean after 24 hours, consider reducing the % wean with each step (e.g. 5% wean Q24H instead of 10% wean Q24H) or increasing the interval between weans (e.g. 10% wean Q48H instead of 10% wean Q24H).
  - If weaning 2 agents at the same time, switch to alternate day weans if both were being weaned daily or consider weaning only one drug at a time.

IV to Enteral Conversion of Opioids, Benzodiazepines and α_2-adrenergic agonists

Full enteral feeds tolerated

Calculate IV to Enteral Conversion

IV Morphine → PO Morphine: __mg/24hr IV Morphine x 3 = __mg/24hr PO Morphine (divide into Q4-6H dosing)

IV Midazolam → PO Lorazepam: __mg/24hr IV Midazolam x 0.1 = __mg/24hr PO Lorazepam (divide into Q6H dosing)

IV Dexmedetomidine Rate	→	PO Clonidine Dose
0.2-0.3 mcg/kg/hr	→	2 mcg/kg/dose Q6H
0.4-0.5 mcg/kg/hr	→	3-5 mcg/kg/dose Q6H

CLINICAL DETERIORATION?
Consider "Exiting" the Algorithm

Differentials for Agitation or ↑WAT-1 score

- Pain
- Hypoxia / Hypercarbia
- Ventilator dyssynchrony
- Sepsis
- Low cardiac output state
- Hypoglycemia
- Feed intolerance
- Itch / Full bladder / Constipation
- Delirium
- Disrupted sleep

Transit from IV to Enteral Formulation

Step 1: Start PO Morphine/Lorazepam/Clonidine at calculated dose
Step 2: Wean IV Morphine/Midazolam/Dexmedetomidine infusion by 50% 30 minutes after the **2nd** PO Morphine/Lorazepam /Clonidine dose
Step 3: Turn off IV Morphine/Midazolam/Dexmedetomidine infusion 30 minutes after the **3rd** PO Morphine/Lorazepam/Clonidine dose
Remember to stagger the timings for conversion and keep same enteral dose for 24 hours*

Wean dose according to original weaning rate (Q24-48H) *

At Minimum enteral dose, wean dosing interval until stopping all sedatives
(Q4H → Q6H →Q8H → Q12H → Q24H → Off)

Agent	Minimum Enteral Dose	Maximum Enteral Dose
PO Morphine	0.1mg/kg/dose	15 mg/dose
PO Lorazepam	0.02mg/kg/dose	2 mg/dose
PO Clonidine	1mcg/kg/dose	5 mcg/kg/dose (100 mcg/dose)

Assess for Withdrawal: WAT-1 score Q8H (Or more frequent if necessary)

Weaning successful
WAT-1 < 3 AND < 2 above baseline

Continue weaning
Monitor WAT-1 score until 72H after last dose of sedatives

Withdrawal suspected

- WAT-1 ≥ 3 AND > 2 above baseline
- Consider differentials for ↑WAT-1 score

Serve Rescue Dose

- Morphine: PO 0.15mg/kg
- Lorazepam: PO 0.05mg/kg

(Serve either drug or both, depending on clinical suspicion)
Hold weaning for 24H
Repeat WAT-1 score in 1H after rescue doses!

WAT-1 < 3

- Continue current regular dosing
- Continue weaning after 24H

WAT-1 ≥ 3

- Consider differentials for ↑WAT-1 score
- Repeat rescue dose
- If ≥ 3 rescue doses given, ↑ to previous dose of sedative last weaned
- Resume wean after 24H, KIV reduce % wean or increasing interval between weans

*Stagger both the timing for enteral conversion and the time for dose weaning for different drug classes

References

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Annex A – IV to IV / Enteral Conversion Calculator for Analgesia and Sedation

OPIOID CONVERSION

Conversion of IV Morphine to PO Morphine	
Body Weight (kg)	
IV Morphine Infusion Rate (mcg/kg/hr)	
Total PO Morphine dose over 24 hrs (mg/24hrs)	0.0
PO Morphine Q6H Dose (mg)	0.0
PO Morphine Q4H Dose (mg)	0.0

Conversion of IV Fentanyl to IV Morphine	
IV Fentanyl Infusion Rate (mcg/kg/hr)	
IV Morphine Infusion Rate (mcg/kg/hr)	0

Conversion of IV Fentanyl to PO Morphine	
Body Weight (kg)	
IV Fentanyl Infusion Rate (mcg/kg/hr)	
Total PO Morphine dose over 24 hrs (mg/24hrs)	0.0
PO Morphine Q6H Dose (mg)	0.0
PO Morphine Q4H Dose (mg)	0.0

BENZODIAZEPINE CONVERSION

Conversion of IV Midazolam to PO Lorazepam	
Body Weight (kg)	
IV Midazolam Infusion Rate (mcg/kg/min)	
Total PO Lorazepam dose over 24 hrs (mg/24hrs)	0.0
PO Lorazepam Q6H Dose (mg)	0.0

Annex B – Acronym Expansion for Daily Sedation Plans

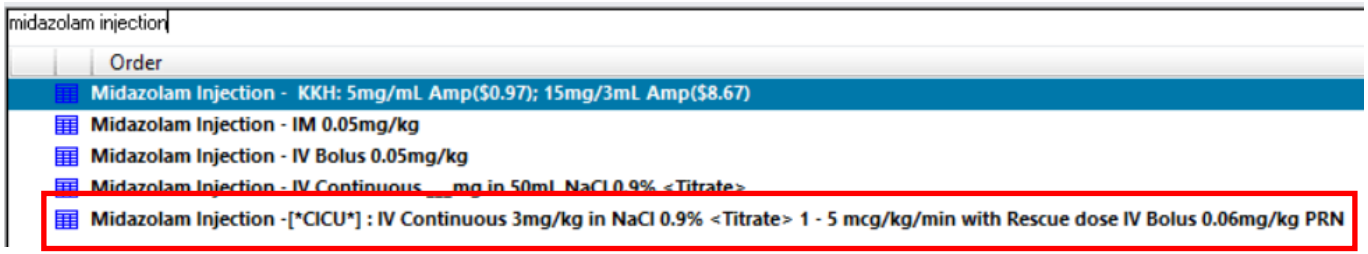
Daily sedation targets and sedation weaning plans should be clearly documented within the doctors' plans. (i.e. CICU Daily Ward Round Note)

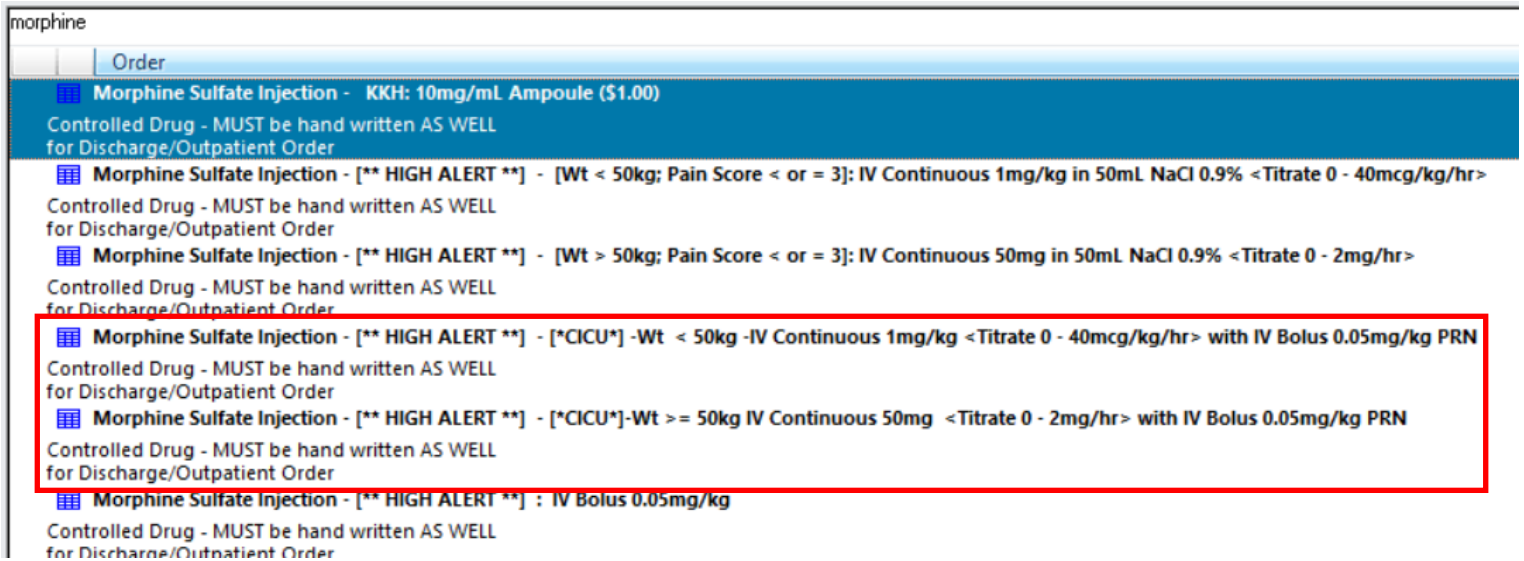
Import the following acronym expansion for "Daily Sedation Plan" from "Lim Kian Boon Joel".

1. Click on "Preferences" → Select "Acronym Expansion" to open your personal "Acronym Expansion Maintenance Dialog"
2. Select "Import From Other User" → In the field for "Select From Existing List", type in and select "Lim Kian Boon Joel"
3. To add the acronym expansion, tick the box on the left for the specific acronym to be added, then click on "OK"

#DSP
-Neuro/Sedation/Analgesia Sedation goal: Target SBS scores ___ to ___ WAT-1 score frequency: Q8H Date/Time sedation weaning started: Original infusion dose when weaning started: i) IV Morphine (mcg/kg/hr) / IV Fentanyl (mcg/kg/hr): ii) IV Midazolam (mcg/kg/min): iii) IV Dexmedetomidine (mcg/kg/hr): Sedation weaning strategy: i) IV Morphine / IV Fentanyl: to reduce by __% / __mcg/kg/hr Q24H ii) IV Midazolam: to reduce by __% / __mcg/kg/min Q24H iii) IV Dexmedetomidine: to reduce by __% / __mcg/kg/hr Q24H (Any patient-specific rescue plan?)

Annex C – Change to IV Morphine and Midazolam Infusion Orders in the CICU





These new order sets for CICU will contain comments within "Order Details/Instructions" to **standardize rescue/prophylactic doses**

- For IV Midazolam → For Rescue/Prophylactic Doses: To administer 0.06mg/kg IV Midazolam PRN (Maximum of 2x per hour)
- For IV Morphine → For Rescue/Prophylactic Doses: To administer 0.05mg/kg IV Morphine PRN (Maximum of 2x per hour)