Inpatient Pediatric Opioid, Benzodiazepine, and Alpha agonist Withdrawal Prevention Guideline

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Guideline Inclusion Criteria

Patients admitted to Dell Children's Hospital who are at risk for withdrawal from opioids, benzodiazepines, and alpha agonists (see risk categories below).

Guideline Exclusion Criteria

Patients in the Neonatal Intensive Care Unit. Patients who are receiving treatment for chronic pain or palliation.

Background

Children admitted to intensive care are frequently exposed to opioid, benzodiazepine, and/or alpha agonist infusions for analgesia and sedation. [1] Owing to the severity of illness of many children, prolonged exposure to these medications frequently occurs, resulting in an increased risk of withdrawal when these medications are no longer required. [2,3] To prevent iatrogenic withdrawal, these medications must be carefully tapered.

The symptoms of withdrawal, which may occur from abrupt discontinuation or tapering medications too quickly, include neurological excitability, gastrointestinal dysfunction, and autonomic dysfunction. [4–6] These symptoms cause physiological and emotional distress for the patients and their families and can lead to prolongation of medication tapering and, potentially, length of stay. [7,8] Currently, significant practice variation exists within and between institutions concerning the weaning of opioids, benzodiazepines, and alpha agonists. [9,10] In the absence of a standardized approach, patients are frequently treated at the discretion of the provider, which can lead to overtreatment or undertreatment of withdrawal. [11–14]

Total exposure, including both duration of therapy and dose, are important determinants of withdrawal risk for opioids, [4,8,9,17–19] benzodiazepines, [19,20] and alpha agonists. [33,34] Our guideline, therefore, incorporates both of these factors in the design of patients' weaning plans. Providers are strongly encouraged to wean patients on stable sedation to the minimal doses required to minimize exposure risk. Weaning is particularly important for patients on long-term sedation (high and ultra-high-risk groups).

In this guideline, risk categories were selected based on a review of our data (Wilson, 2021) and experience at DCMC, along with an extensive review of the literature and protocols currently employed by other children's hospitals (see External Guidelines/Clinical Pathways Reviewed).

Withdrawal Risk Criteria:

Risk of withdrawal relative to duration of exposure to continuous infusions

- Minimal Risk ≤ 3 days
- Low Risk > 3-5 days
- Moderate Risk > 5-10 days
- High Risk > 10-21 days
- Ultra High Risk > 21 days

Besides duration and total dose, other factors such as age and cognitive impairment affect the risk of withdrawal,[9] so making a "one size fits all" approach to weaning dose and duration is impossible. Therefore, the guideline includes prescribed steps to manage withdrawal and oversedation to allow rapid interventions by bedside providers and prescribers, which is essential for patient comfort and safety. In addition, certain populations are at increased risk of deterioration if withdrawal occurs, and providers should consider consulting with unit pharmacists in these cases. At-risk groups include patients with:

- Seizure disorders
- Hemodynamically significant congenital heart disease
- Pulmonary hypertension
- History of complications from withdrawal

The rationale for the choice of weaning medications

Opioids

Although several medications can be used to treat withdrawal symptoms, methadone was selected in this guideline because of its favorable characteristics, including its enteral route of administration and long half life, which minimizes dosing frequency.

Benzodiazepines

We similarly chose lorazepam as it may be administered enterally, has fewer drug interactions, and lacks active metabolites compared with diazepam. [3]

Dexmedetomidine (alpha agonist)

Like most other pediatric and adult centers, we selected enteral clonidine as our weaning medication. [36,38] Transdermal patch administration has been studied in a few centers [33, 34] and is an alternative in a select group of patients (see criteria below).

Conversion of infusions to weaning medications

Patients requiring weaning (on > 5 days of infusions) are converted to intermittent weaning medications as described below. Starting doses of medications should be calculated from the respective infusion rate the patient received for at least 12 consecutive hours in the previous 24 hours. These conversions consider differences between the agent's potency, half-life, and oral bioavailability. [3]

Opioids

Providers should exercise caution when converting current opioid infusions to methadone. Equianalgesic dose conversions are estimates and do not account for individual variability in genetics and pharmacokinetics. Methadone has a long and variable half-life, and the peak respiratory depressant effect occurs later and lasts longer than the peak analgesic effect. [39] The conversions outlined here are based on the review of 177 patients at Dell Children's Hospital [42] and a review of the literature.

Fentanyl

To convert Fentanyl infusion to methadone, 50% of the equipotent dose [14] is used to account for methadone's long half-life and high bioavailability. Specifically, the hourly rate of fentanyl (mcg/kg/hr) is multiplied by 0.05 to determine the starting dose of methadone (mg/kg), max 0.2 mg/kg, never more than 10 mg, which is dosed every 6 hours.

Morphine

For morphine infusions, the hourly rate (mg/kg/hr) is multiplied by 0.5 to determine the starting dose of methadone (mg/kg), max 0.2 mg/kg, never more than 10 mg. This dose is dosed every 6 hours and incorporates 50% of the equipotent dose. This approach is a more conservative conversion than we proposed in our original guidelines based on more recent published protocols [12,13] and subsequent experience.

Hydromorphone

Our institution has increasingly favored hydromorphone over morphine for analgesia and analgosedation due to its low risk of side effects and decreased tachyphylaxis. To convert from hydromorphone, we converted to morphine equivalents. We then followed the conversion to methadone described above using a conversion of the hourly rate (mg/kg/hr) multiplied by 3.4 to determine the starting dose of methadone (mg/kg), max 0.2 mg/kg, never more than 10 mg, which is dosed every 6 hours. [47] This conversion incorporates a 50% dose reduction from the equipotent dose. Of note, because of its longer half-life, providers may consider weaning hydromorphone infusions with every other dose of methadone in patients with prolonged exposure.

Benzodiazepines

For midazolam infusions, the hourly rate (mg/kg/hr) is multiplied by 0.5 to determine the starting dose of lorazepam (mg/kg) every 6 hours. [3] A maximum dose of 0.2 mg/kg/dose and never more than 4 mg/dose was used.

Dexmedetomidine

There is limited data on how to convert dexmedetomidine to clonidine. In one study, patients who received an average infusion of 1 mcg/kg/hour of dexmedetomidine, a clonidine dose of 9 mcg/kg per day given via transdermal patch, was needed to prevent withdrawal symptoms. [33] Non-published protocols use similar doses in the range of 8-12 mcg/kg/day for all patients regardless of infusion rate or a range of 8-12 mcg/kg/day for patients receiving 0.6-1 mcg/kg/hr or 12 mcg/kg/day exposed to infusions of > 1.1 mcg/kg/day (CHLA, Cleveland Clinic, Childrens Nebraska, Duke). Based on our experience over the past ten years at DCMC, we recommend a dose of 8 mcg/kg/day for the low-dose group and 12 mcg/kg/day for the high-dose group. In patients who are on > 1.5 mcg/kg/hr and are at high risk of hemodynamic instability, providers should strongly consider weaning the infusion to <1.5 mcg/kg/hr so a lower dose of clonidine can be utilized. Based on adult literature, a maximum dose of 0.2 mg/dose of oral clonidine should be used for the low-dose group and 0.3 mg/dose for the high-dose group. [36, 34, 37]

Conversion Enteral to IV for patients unable to tolerate the enteral route

If the patient can not tolerate enteral lorazepam, the same dose can be given intravenously for both based on its high oral bioavailability. [26] For Methadone, we recommend an oral-to-IV ratio of 1:0.8 based on current literature. [40, 43] Clonidine may be converted to a transdermal patch using a 1:1 conversion based on the total daily dose. Due to patch size, they are best suited to children calculated to receive > 50 mcg /day due to difficulty in proper dosing due to patch sizes. If a patch is chosen, providers should consult with the pharmacy.

1. Patches **can not be cut**. To administer a half patch, place a Tegaderm underneath 50% of the patch.
2. Use the conversion as described for enteral clonidine to calculate the total daily dose for the patch.
3. The dose may need to be rounded to available patch sizes. For example, for a patient on 15 mcg q6, the total daily dose is 60 mcg. Therefore, the closest patch size would be half of a 0.1 mg patch (50 mcg)
4. Place the patch 48 hours before weaning off Dexmedetomidine, as this is the time required to achieve a steady-state clonidine concentration via the patch.
5. RNs should verify patch placement q 12h.
6. If the patient is oversedated, remove the patch and discuss the plan with the pharmacy.
7. If the patient has signs of withdrawal, give enteral PRN clonidine per withdrawal algorithm and discuss the change in patch dose with the pharmacy if needing frequent PRNs.
8. In the moderate-risk group, the patch may be removed after one week. Discuss with the pharmacist to determine an individualized weaning plan for patients in the high and ultra-high-risk groups.

Timing of Conversion to weaning medications

Weaning medications, particularly methadone, which has a long half-life, should be started at least 24-48 hours prior to extubation, depending on the length of exposure. Once initiated, infusions should be weaned per the weaning algorithm.

In some situations, providers may consider leaving dexmedetomidine on through extubation without starting clonidine, particularly if the patient may require non-invasive ventilation. If clonidine is started later, consider stopping dexmedetomidine at the time enteral clonidine is started or a rapid wean of 50% with each dose to avoid the risk of oversedation in extubated patients.

With all weaning medications, If a patient's status changes and providers are not planning to extubate, we recommend resuming infusion medications and discontinuing weaning medications to prevent dual therapy.

Tapering of weaning medications

Once patients were stable on weaning medications for 24 hours with (WAT-1) scores < 3 and off continuous infusions, providers should begin weaning the medications based on the patient's risk category.

Please see the wean algorithm for details on how to wean medications. Due to methadone's longer half-life, some providers may consider consolidating the same TOTAL daily dose earlier to less frequent dosing (e.g., moving from q6h to q8h, then q12 h more rapidly). However, this should be done cautiously as higher, less frequent doses can lead to oversedation. Please contact your pharmacist for assistance.

Identification of iatrogenic withdrawal syndrome (IWS)

IWS occurs when sedation and analgesic medications are stopped, weaned rapidly, or chemically reversed after prolonged exposure. IWS symptoms tend to be non-specific and may be driven by autonomic dysfunction secondary to sympathetic activation (tachypnea, tachycardia, elevated temperature, and diaphoresis), gastrointestinal symptoms (vomiting and diarrhea), alterations within the central nervous system (agitation, trembling, seizures, and delirium). Commonly reported symptoms by each class include:

Opioid: Gastrointestinal (diarrhea, vomiting, feeding intolerance), central nervous system (tremors, seizures, agitation, insomnia, yawning, sneezing), and sympathetic hyperactivity / autonomic dysfunction (tachycardia, diaphoresis, hypertension, tachypnea, nasal stuffiness, hyperpyrexia)

Benzodiazepine: Central nervous system (agitation, restlessness, irritability, delirium, hallucinations, seizures) and sympathetic hyperactivity (tachycardia, hypertension, tachypnea, hyperpyrexia)

Alpha-agonist: Tachycardia, hypertension, agitation, tremors, increased muscle tone, and insomnia,[34] with vomiting, diarrhea, and fever occasionally noted.[35]

Depending on the medication's half-life and other factors, such as whether it has active metabolites, the onset of IWS may be delayed up to 48 to 72 hours after discontinuation or weaning medications.

WAT-1 Tool is validated for pediatric patients to aid clinicians in the recognition of clinically significant opioid or benzodiazepine withdrawal symptoms to guide the treatment of IWS. [6] Patients at low or higher risk of withdrawal should be scored q 6h to 12hs. Withdrawal typically occurs within 48 hours and is unlikely if there has been no wean in the previous 72 hours. [44] Withdrawal should be considered if the patient's WAT-1 score is ≥ 3. [6] If a patient has preexisting conditions such as hypertonia, tremor, diarrhea, emesis, and hypertonia) providers should choose a higher WAT-1 score. For example, providers are encouraged to change the reportable/actionable WAT-1 score to ≥ 5 in patients with baseline tremor and hypertonia.

Vital Signs For patients at risk of withdrawal from dexmedetomidine, providers should also monitor heart rate and blood pressure and consider withdrawal if these parameters are greater than 20% above the patient's baseline, as tachycardia and hypertension are not evaluated by WAT-1 and have been associated with alpha agonist withdrawal. [48]

Management of withdrawal

If a patient's WAT-1 score and/or vital signs are suggestive of withdrawal, providers should assess the patient to rule out other causes, such as sepsis, cardiac failure, respiratory distress, or gastrointestinal problems. As there is a significant overlap in withdrawal symptoms between opioids, benzodiazepines, and alpha agonists,[41] once withdrawal is suspected, the likely agent should be determined by reviewing the patient's symptoms and medication history to determine which medication was most recently weaned.

If the WAT-1 score ≥ 3 or > 2 above baseline and presentation is consistent with withdrawal after considering other causes for symptoms, administer a rescue dose of medication as outlined in the withdrawal/over-sedation algorithm. Reassess WAT-1 score in 1 hour. If WAT-1 is still high, consider repeating the dose of the initial medication (if there is a partial response) or giving a rescue dose of other weaning medication if applicable (i.e., Lorazepam or Clonidine)

If the provider is unable to determine the causative agent of withdrawal based on symptoms, vital signs, and history, we recommend using rescue medications in the following order: morphine> Clonidine> Lorazepam.

Identification and Management of Over Sedation

If excessive sedation is apparent on clinical assessment, including Pasero Opioid-induced Sedation Scale (POSS) > 2 (e.g. patient is frequently drowsy, arousable but drifts off to sleep during conversation) or Richmond Agitation–Sedation Scale (RASS) < - 1, after beginning weaning medications, the provider should consider holding all weaning medications until the patient is stable and then decreasing the dose of the medication associated with the onset of symptoms according to the next step recommended in the patient's weaning plan. If the patient is on the medication's starting dose, consider decreasing the dose by 20%.

Important: EHR Documentation and Ordering

Providers should enter the medication orders using the opioid, benzodiazepine, and alpha agonist weaning plan (PEDI). They should update the medication doses as the patient progresses on the weaning plan to avoid failure to progress.

When weaning multiple agents, it is best to alternate the medications. It is important to space out the weaning steps, especially for ultra-high-risk patients, to identify which medication is causing withdrawal symptoms. Additionally, there is a need to space medication administration to avoid overlapping doses, which increase the risk of oversedation and risk for hypotension. For example, if weaning clonidine, lorazepam, and methadone and all are given q6h, time them so there are 2 hours between doses.

The patient's medication history (length of infusion, rate used for conversion to wean medication) and weaning plan with updates should be documented in the EHR. Any provider amending the plan should add a comment with the rationale for the change and the proposed updated weaning schedule.

External Guidelines/Clinical PathwaysReviewed

Organization	Date accessed
Cleveland Clinic	1/24
CHLA	9/23
CCU CHOP	9/23
PICU CHOP	9/23
Stanford	9/23
Minnesota Children's Hospital	9/23
Norton Children's	9/23
University of Washington	9/23
Duke University	9/23
STARSHIP Hospital	5/24

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