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Prevention and Treatment of Opioid and Benzodiazepine Withdrawal

Version: 3

1.0 Introduction

This guideline provides clinicians with practice recommendations intended to promote a consistent, evidence-based approach to the prevention and management of iatrogenic withdrawal syndrome in patients who are being weaned off opioids and/or benzodiazepines. The document was developed by a multidisciplinary group of health care providers and is based on published evidence, existing clinical practice guidelines, and expert consensus.

1.1 Target Patient Population

These guidelines are intended for patients outside of critical care environments at risk of withdrawal from opioids and/or benzodiazepines when the pharmacological effects of these medications are no longer required.

Patients at increased risk of iatrogenic withdrawal include those who have received:

- Opioid infusion or regular dosing for 5 days or more, and/or
- Benzodiazepine infusion or 3 doses or more per day for 5 days or more

These guidelines may be useful in situations where opioids/benzodiazepines were administered for less than 5 days. Evidence suggests symptoms of withdrawal can develop after as little as 3 days of very high dose therapy.

These guidelines are *not* intended for:

- Neonates with antenatal exposure to opioids and/or benzodiazepines.
- Management of substance use disorders or opioid use disorders.

1.2 Target Users

These guidelines are intended for members of the nursing team (including RNs, APNs), the medical team (including Physicians, Physician Assistants) and Pharmacists.

Acute Pain Service (APS) involvement is not required for every opioid and/or benzodiazepine weaning plan, however, consider contacting APS for guidance with patients who are at high- or very high-risk of withdrawal, or if symptoms of withdrawal develop despite following these guidelines.

1.3 Definitions

- **Physical dependence** is defined as an adaptive state in which cessation of a medication results in signs and symptoms of withdrawal.
- **Tolerance** is defined as a state of adaptation in which exposure to a medication results in lessening of the effects of the drug, necessitating an increased dose to produce the same analgesic or sedative effect.
- **Iatrogenic Withdrawal Syndrome (IWS)** includes the physical signs and symptoms that manifest when an opioid or benzodiazepine is stopped abruptly or weaned too quickly after prolonged use. IWS may occur with the usage of these agents for as short as five consecutive days or occasionally even after only three days. The onset and course of the withdrawal state are related to dose and type of medication.

1.4 Agents associated with withdrawal

Commonly used agents associated with withdrawal symptoms include opioids, benzodiazepines, alpha-2 adrenergic agonists (clonidine, dexmedetomidine) barbiturates and chloral hydrate. This guideline addresses management of withdrawal associated with opioids, benzodiazepines, and clonidine.

1.5 Risk factors for iatrogenic withdrawal syndrome

- Use of opioids and/or benzodiazepines for ≥5 days
- Higher cumulative and/or peak doses, and use of multiple agents associated with withdrawal
- Patients with previous experience of withdrawal
- Younger age, with some evidence of higher risk at age < 6 months
- Pre-existing cognitive or functional impairment

Sex, diagnosis, and severity of illness are not associated with increased risk of withdrawal. There is no strong evidence that withdrawal risk differs based on type of opioid.

2.0 Assessment and Diagnosis of Withdrawal

2.1 Signs and Symptoms of Withdrawal

Signs of symptoms of withdrawal (Table 1) may manifest as Central Nervous System alterations, gastrointestinal dysfunction, and/or autonomic activation/dysfunction.

Table 1. Common symptoms of withdrawal

	Opioids	Benzodiazepines	Alpha-2 adrenergic agonists
Tremors	✓	✓	
Restlessness, irritability	✓	✓	
Agitation		✓	✓
Insomnia	✓	✓	
Dysphoria	✓	✓	
Delirium or hallucinations		✓	
Seizures		✓	
Anxiety	✓	✓	
Involuntary movements		✓	✓
Hypertonicity			✓
Nausea, vomiting	✓	✓	
Diarrhea, loose stool	✓		
Tachypnea	✓		
Tachycardia	✓	✓	✓
Hypertension	✓		✓
Perspiration	✓	✓	
Sneezing, rhinorrhea, yawning, piloerection	✓		
Fever	✓		
Mydriasis (dilated pupils)	✓		

Many of these signs and symptoms may be attributed to other underlying conditions (e.g. inadequate sedation, sepsis, cardiovascular or neurologic pathology, delirium), and thus withdrawal is *a diagnosis of exclusion.* It is often difficult to determine which medication is contributing to withdrawal. Benzodiazepine and opioid withdrawal can present very similarly.

Onset of withdrawal symptoms after cessation of opioids/benzodiazepines:

- Variable from hours to days, dependent on medication duration of action
- May occur within hours for a short-acting opioid like fentanyl but may be delayed for medications like methadone or longer acting benzodiazepines by days or over a week.
- Can be delayed for medications with active drug metabolites (e.g. morphine, diazepam) or in the setting of renal or hepatic dysfunction.

2.2 Assessment of Withdrawal using the WAT-1

The WAT-1 is a validated tool for the assessment of symptoms of withdrawal related to the weaning of opioids and benzodiazepines. Appendix 1: Withdrawal Assessment Tool

When using the WAT-1 the following factors should be taken into consideration:

- Natural course of patient's illness.
- Patient baseline.
- Other potential contributing factors (e.g. environment).
- Scores should be interpreted on their trend over time.

Use of the WAT-1

- Obtain a baseline withdrawal score using the WAT-1 before any of the medications are weaned.
  - If a patient has features or symptoms that would result in a score on the WAT-1 tool *prior* to weaning (e.g. diaphoresis, loose stool, low-grade fever), the patient does not receive a score for those features on the WAT-1 when weaning unless the baseline symptoms worsen/increase in frequency.
- Assess and document pain intensity as per hospital policy and orders (Refer to Pain Assessment)
- Obtain a WAT-1 score every 12 hours at 06:00 and 18:00, or more frequently if ordered.
  - More frequent assessment (e.g. q6h) may be necessary (e.g. if withdrawal scores are high and intervention is required) and is based on clinical judgement.
- WAT-1 scores >3 or increasing trends in the scores may indicate withdrawal but patient should be assessed to rule out other contributing causes of the increased score.
- Inform ordering provider if scores are > 3 or trending upwards. Refer to Tables 2 and 3 to direct ongoing management.
- Continue scoring minimum q12h until 72 hours after the patient's last required dose of opioid/benzodiazepine.

3.0 Opioid and Benzodiazepine Weaning Practice Recommendations

3.1 Initial Steps

- A decision to wean sedative and analgesic medications is based on the clinical condition of the child and takes into consideration a) all analgesics and sedatives ordered including all regular and PRN dosing, b) the ongoing need for these medications, and c) the duration of their use.
- Prior to weaning any opioid and/or benzodiazepine, WAT-1 scoring should be ordered minimum q12h.

Order of medications to wean:
For patients with both opioids and benzodiazepines requiring a wean, the general recommendations are:

- Wean opioid until at 50% of original dose (See Table 2).
- Begin weaning benzodiazepine dose once opioid is at 50% of its original dose (See Table 3).
- Continue daily opioid and benzodiazepine wean (following Tables 2 and 3).
- If on clonidine, this should not be weaned until the opioid and benzodiazepine have been successfully discontinued (See Section 4.5).
- Weaning from more than one medication can be done simultaneously, however if there are signs or symptoms of withdrawal, consider modifying the plan:
  - Wean medications simultaneously, but on alternating days, or,
  - Wean one medication completely before beginning the next medication wean.

Note: Above is a general guideline and will need to be tailored to patient's clinical situation. For example, it may be more important to wean the benzodiazepine first if there is an ongoing requirement for analgesia.

3.2 Opioid and Benzodiazepine Weaning Guidelines

The following tables have been developed to help guide the weaning process with the aim of prevention of withdrawal symptoms. If the patient has been exposed to opioids and/or benzodiazepines for 5 days or more on a regular basis then weaning is recommended to reduce risk of withdrawal.

- For patients who require weaning of opioids only, follow Table2..
- For patients who require weaning of benzodiazepines only, follow Table 3.
- For patients who require weaning of both opioids and benzodiazepines, refer to Section 3.1 for order of medications to wean, and follow steps in both Tables 2 and Table 3.

  Once at low doses, weaning continues by increasing the interval between the doses rather than reducing the dose further. See Table 4. Note: As with all clinical practice guidelines, individual patients may require deviation from this guideline. Clinical judgement is required. Consult APS for support if required.

Table 2: Opioid Weaning Guidelines

<table>
<tr><th colspan="4">1. Assess Withdrawal Risk</th></tr>
<tr><td>Low Risk: Continuous opioids < 5 days</td><td>Moderate Risk: Continuous opioids 5-10 days and age >6 months</td><td>High Risk: Continuous Opioids >10-27 days, or >5 days for age <6 months</td><td>Very High Risk: Continuous opioids >27 days</td></tr>
<tr><td rowspan="13">No wean. No scheduled opioids required.</td><td colspan="3">2. Withdrawal Assessment (Section 2.0)</td></tr>
<tr><td colspan="3">• Order WAT-1 scoring minimum q12h. Score >3 may indicate withdrawal.</td></tr>
<tr><td colspan="3">3. Enteral Conversion (Section 3.3)</td></tr>
<tr><td colspan="3">• Convert opioid to oral equivalent as early as possible.</td></tr>
<tr><td colspan="3">4. Rescue Medication</td></tr>
<tr><td colspan="3">• Order PRN dose of medication* being weaned to be given if WAT-1 >3 on two consecutive assessments.</td></tr>
<tr><td colspan="3">5. Weaning Plan</td></tr>
<tr><td>• Moderate risk: Wean by 20% of original opioid dose q24h</td><td colspan="2">• High/Very High Risk: Wean by 10% of original opioid dose q24h. Consider methadone taper. Consider contacting APS. (See Section 4.6)</td></tr>
<tr><td colspan="3">• Wean dose until values specified in Table 4. Then begin increasing dosing interval.</td></tr>
<tr><td colspan="3">6. Withdrawal Management Plan (Section 4.3)</td></tr>
<tr><td colspan="3">• If WAT-1 >3 on two consecutive assessments, hold the wean. Give rescue dose and reassess.</td></tr>
<tr><td colspan="3">⇩</td></tr>
<tr><td>If 0-2 rescue doses required in 24h:</td><td>If >2 rescue doses required in 24h and rescue doses reduced WAT-1 score:</td><td>If >2 rescue doses required in 24h and rescue doses did not reduce WAT-1 score:</td></tr>
<tr><td>• Continue weaning once symptoms resolve. Consider increasing frequency of WAT-1 assessments.</td><td>• Increase back to last tolerated dose.
• Hold wean for 24h. Once symptoms resolve, resume wean at slower rate (Section 3.4). Consider increasing frequency of WAT-1 assessments.</td><td>• Consider other sources of high WAT-1 score (e.g. infection, change in clinical status)
• Continue to wean after other sources have been investigated</td></tr>
</table>

*Dose suggestions: 50% of scheduled enteral dose, or 1-2h worth of IV infusion dose (e.g. if weaning 10mg morphine q4h, order 5mg q2-4h PRN for WAT-1 >3. If weaning 30 mcg/kg/hr, order 30-60mcg/kg q2-4h PRN for WAT-1 >3).

Table 3: Benzodiazepine Weaning Guidelines

<table>
<tr><td colspan="4">1. Assess Withdrawal Risk</td></tr>
<tr><td>Low Risk: BZD <3 doses/day or for < 5 days</td><td colspan="2">Moderate Risk: BZD ≥ 3 doses/day for ≥ 5 -10 days or BZD infusion ≥ 5-10 days</td><td>High Risk: BZD ≥ 3 doses/day for > 10 days or BZD infusion > 10 days</td></tr>
<tr><td rowspan="11">No wean. No scheduled opioids required.</td><td colspan="3">2. Withdrawal Assessment (Section 2.0)</td></tr>
<tr><td colspan="3">• Order WAT-1 scoring minimum q12h. Score >3 may indicate withdrawal.</td></tr>
<tr><td colspan="3">3. Enteral Conversion (Section 3.3)</td></tr>
<tr><td colspan="3">• Convert BZD to oral equivalent as early as possible.</td></tr>
<tr><td colspan="3">4. Rescue Medication</td></tr>
<tr><td colspan="3">• Order PRN dose of medication* being weaned to be given if WAT-1 >3 on two consecutive assessments.</td></tr>
<tr><td colspan="3">5. Weaning Plan</td></tr>
<tr><td colspan="2">• Moderate risk: Wean by 20% of original BZD dose q24h</td><td>• High risk: Wean by 10% of original BZD dose q24h.</td></tr>
<tr><td colspan="3">• Wean dose until values specified in Table 4. Then begin increasing dosing interval.</td></tr>
<tr><td colspan="3">6. Withdrawal Management Plan (Section 4.3)</td></tr>
<tr><td colspan="3">• If WAT-1 >3 on two consecutive assessments, hold the wean. Give rescue dose and reassess.</td></tr>
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<tr><td>If 0-2 rescue doses required in 24h:</td><td>If >2 rescue doses required in 24h and rescue doses reduced WAT-1 score:</td><td>If >2 rescue doses required in 24h and rescue doses did not reduce WAT-1 score:</td></tr>
<tr><td>• Continue weaning once symptoms resolve. Consider increasing frequency of WAT-1 assessments.</td><td>• Increase back to last tolerated dose.
• Hold wean for 24h. Once symptoms resolve, resume wean at slower rate (Section 3.4)
• Consider increasing frequency of WAT-1 assessments.</td><td>• Consider other sources of high WAT-1 score (e.g. delirium, change in clinical status)
• Continue to wean after other sources have been investigated</td></tr>
</table>

*Dose suggestions: 50% of scheduled enteral dose (e.g. if weaning 5 mg diazepam q6h, order 2.5mg 4h PRN for WAT-1 >3.)

Table 4: Weaning dose limits (enteral) and frequency

Medication	Minimum enteral dose: Dose below which interval should be extended*	Dosing intervals once minimum dose is reached	Frequency of dose interval increase
Morphine	0.1 mg/kg q4h	q6h, q8h, q12h, q24h	Each step should be for the same time period that was followed during dose weaning. E.g. If dose was weaned every 48h, the dosing interval will increase every 48h.
Hydromorphone	0.02 mg/kg q4h		
Diazepam**	0.05 mg/kg q6h	q8h, q12h, q24h	

*i.e. Wean dose until this dose is reached
** For other oral benzodiazepines the suggestion is to wean until the lowest dose that is simple to administer/dispense is reached based on tablet/capsule/syrup availability and patient weight. Then, increase the dosing interval as described above.

3.3 Conversion to Enteral Dosing

- An early goal in weaning should be to convert all analgesics and sedatives to enteral formulation. This should be done as early as possible once a patient is able to tolerate enteral medications and not likely to have significant periods of being nil by mouth.
- Refer to the Opioid Equianalgesic Conversion Chart to guide conversion between IV and Enteral opioids. See Appendix 2 for conversion examples for both opioids and benzodiazepines. Once enteral formulation has been established, continue the same % wean that was being weaned while in IV form.

3.4 Reducing Wean Frequency

It may be necessary to reduce the frequency of weaning if signs and symptoms of withdrawal develop. This may happen at any time throughout a wean but is more likely to occur as smaller doses are reached. If this is the case, you may need to slow the wean.
Some suggestions would be:

- Dropping the % wean: e.g. 5% wean every 24hours instead of 10% wean.
- Increasing the interval between weans: e.g. going from q24h to q48h.
- If weaning opioids and benzodiazepines: wean off one drug at a time or switch to alternate day weans if both were being weaned daily.

4.0 Management of Opioid and Benzodiazepine Withdrawal Practice Recommendations

4.1 Key Points

- Refer to Section 2.0 for recommendations related to assessing and diagnosing Iatrogenic Withdrawal Syndrome.
- Holding a wean requires an assessment of the trend of rescue (PRN) medication over the previous 24-48h period. A wean should not necessarily be held based on a single WAT-1 score or single rescue dose.
- Reasons for increased WAT-1 scores, irritability, or agitation apart from withdrawal should be considered.
- A successful opioid/benzodiazepine wean depends upon careful observation and regular communication about a patient's needs, goals of care, readiness for enteral medications, and strategies for management including nonpharmacological techniques

4.2 Non-Pharmacological measures to reduce withdrawal

Reduce environmental stimuli at patient's bedside including noise, light and handling.

- Swaddle infants tightly. Some infants may settle with holding, rocking and a pacifier.
- Frequent feedings.
- Appropriate fluid therapy to prevent dehydration.

4.3 Pharmacological recommendations to treat withdrawal

If withdrawal is suspected:

- Give a rescue dose of the medication being weaned and assess for resolution of symptoms.
- If > 2 doses of rescue medication are required in a 24h period *and* the rescue doses resulted in the resolution of withdrawal symptoms, increase the dose of the agent being weaned back to the previous dose where there were no withdrawal symptoms. Hold the wean for 24h.
- Once symptoms have resolved, resume the wean at a slower rate.
- If concurrently weaning opioid and benzodiazepine, consider holding benzodiazepine wean until opioids are weaned off, or weaning the medications on alternate days.
- Adjuncts to assist with weaning should only be added once above has failed.
- When a rescue medication is given to manage symptoms of withdrawal, the same medication being weaned should be used as the rescue medication. E.g. Opioid withdrawal should be treated with opioid replacement therapy. Benzodiazepine withdrawal should be treated with benzodiazepine replacement therapy.

4.4 Adding Adjuncts to assist with weaning of opioids and benzodiazepines

- This should not be used as an initial step. Any adjunct that is added will result in another medication that needs to be weaned for the patient and hence increase time on medications, so should only be used if necessary. Initial management is to slow the wean as outlined above.
- Adjuncts used in non-critical care areas that *may* reduce symptoms of withdrawal include:
    - Clonidine, an alpha2-adrenergic receptor agonist
    - Benzodiazepines (e.g. Diazepam) – if not already on it or increasing the dose if already on it.
- Refer to formulary guidelines for dosing suggestions. Note that for management of withdrawal, dosing frequency may differ from that recommended for sedation purposes for both clonidine and diazepam. Dosing frequencies of no more often than q6h are often recommended when these medications are added as weaning adjuncts.

4.5 Weaning Clonidine

- When clonidine is part of the analgesic/sedative combination, then this should be the last medication to wean. This is because clonidine may help to facilitate weaning of opioids and benzodiazepines.

- The clonidine dose should remain the same until opioid and/or benzodiazepine is completely weaned off.
- Clonidine should be weaned over 7-10 days to avoid rebound hypertension.
- Suggestion for wean:
    - Wean down to 1mcg/kg per dose every 6 hours and then increase the interval between doses to q 8 hours, q 12hours and then q 24hours then cease.
    - Each step would be for 24 hours.
    - Note: Some patients may be on clonidine as part of their management for their underlying disease or health condition. In these patients, clonidine should not be weaned.
- See Appendix 3: Adjuncts to Weaning

4.6 Methadone for Opioid Withdrawal

Methadone is increasingly used for managing acute, complex pain in pediatric patients and as a transition medication when weaning short-acting opioids following sedation in the intensive care setting.
Benefits include:

- Potent analgesic properties through multiple mechanisms including action on opioid receptors, NMDA receptor antagonism, and mild increases in norepinephrine and serotonin levels,
- Long half-life (12-24h) and good bioavailability as an enteral medication enables smooth transition from intravenous opioid infusions to oral dosing that can be as infrequent as every 8 to 12 hours, and decreased dependence on intravenous infusions
- Rich mechanistic actions of methadone help to avoid tachyphylaxis and tolerance that is often seen with continuous intravenous infusions of opioids that are commonly used (fentanyl, hydromorphone and morphine) and makes it an ideal agent for patients who are simultaneously being weaned from high opioid doses but also requiring ongoing analgesia for iatrogenic reasons such as procedures, cares and surgery.

Given the complexity of such conversions, it is advised that patients who are already on methadone in Critical Care areas or who require conversion to methadone on the wards receive consultation from the Acute Pain Service.

5.0 Related Documents

Appendix 1 - Withdrawal Assessment Tool (WAT-1).pdf

Appendix 2 - Conversion Calculations.pdf

Appendix 3 - Adjuncts to weaning.pdf

Pain Assessment

6.0 Guideline Group and Reviewers

Internal Reviewers and 2025 Guideline Update Members:

1. Jacqueline Hanley, Clinical Nurse Specialist, Acute Pain Service
2. Deepa Kattail, Staff Anesthesiologist, Anesthesia and Pain Medicine
3. Ashley Harvey, Clinical Nurse Specialist, Acute Pain Service
4. Carol McNair, Nurse Practitioner, Neonatal Intensive Care
5. Barbara Couper, Clinical Manager, Pain Medicine
6. Carolyn Beck, Staff Physician, Pediatric Medicine
7. Lisa Honeyford, Interprofessional Education Specialist

Original Guideline Group Membership:

1. Haifa Mtaweh, Staff Physician, Critical Care Department,
2. Karen Wong, Pharmacist , Critical Care Department
3. Angie Thiessen, Pharmacist, Critical Care Department
4. Roxanne Kirsh, Staff Physician, Critical Care Department
5. Carol McNair, Nurse Practitioner, Neonatal Intensive Care

References

1. Albertson, T. E., Chenoweth, J., Ford, J., Owen, K., & Sutter, M. E. (2014). Is it prime time for alpha2-adrenocepter agonists in the treatment of withdrawal syndromes?. *Journal of medical toxicology*, *10*, 369-381.
2. Anand Kjs. Et Al. (2010). Tolerance and withdrawal from prolonger opioid use in critically ill children. Pediatrics. 125(5), 1208-25.Berens, R. J., Meyer, M. T., Mikhailov, T. A., Colpaert, K. D., Czarnecki, M. L., Ghanayem, N. S., ... & Weisman, S. J. (2006). A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. *Anesthesia & Analgesia*, *102*(4), 1045-1050.
3. Best, K. M., Boullata, J. I., & Curley, M. A. (2015). Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: a systematic review and conceptual model. *Pediatric Critical Care Medicine*, *16*(2), 175-183.
4. Best, K. M., Wypij, D., Asaro, L. A., & Curley, M. A. (2017). Patient, process, and system predictors of iatrogenic withdrawal syndrome in critically ill children. *Critical Care Medicine*, *45*(1), e7-e15
5. Bichaff, P., Setani, K. T., Motta, E. H., Delgado, A. F., Carvalho, W. B., & Luglio, M. (2018). Opioid tapering and weaning protocols in pediatric critical care units: a systematic review. *Revista da Associação Médica Brasileira*, *64*, 909-915.
6. Birchley, G. (2009). Opioid and benzodiazepine withdrawal syndromes in the paediatric intensive care unit: a review of recent literature. Nursing in Critical Care. 14(1), 26-37.
7. Chiu, A. W., Contreras, S., Mehta, S., Korman, J., Perreault, M. M., Williamson, D. R., & Burry, L. D. (2017). Iatrogenic opioid withdrawal in critically ill patients: a review of assessment tools and management. *Annals of Pharmacotherapy*, *51*(12), 1099-1111.
8. da Silva, P. S. L., Reis, M. E., Fonseca, T. S. M., & Fonseca, M. C. M. (2016). Opioid and benzodiazepine withdrawal syndrome in PICU patients: which risk factors matter?. Journal of Addiction Medicine, 10(2), 110-116.
9. Franck Ls. Et Al (2012) Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. Pain 153(1), 142-8.
10. Honey Et Al. (2009). Alpha-2 Receptor Agonists for Treatment and Prevention of Iatrogenic Opioid Abstinence Syndrom in Critically Ill Patients. The Annals of Pharmacotherapy, 43, 1506-1511
11. Sanchez-Pinto, L. N., Nelson, L. P., Lieu, P., Koh, J. Y., Rodgers, J. W., Larson, K. A., ... & Amirnovin, R. (2018). Implementation of a risk-stratified opioid weaning protocol in a pediatric intensive care unit. Journal of Critical Care, 43, 214-219.
12. Smith, H. A., Besunder, J. B., Betters, K. A., Johnson, P. N., Srinivasan, V., Stormorken, A., ... & Berkenbosch, J. W. (2022). 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. Pediatric Critical Care Medicine, 23(2), e74-e110.
13. Sneyers, B., Duceppe, M. A., Frenette, A. J., Burry, L. D., Rico, P., Lavoie, A., ... & Perreault, M. M. (2020). Strategies for the prevention and treatment of iatrogenic withdrawal from opioids and benzodiazepines in critically ill neonates, children and adults: a systematic review of clinical studies. Drugs, 80, 1211-1233.
14. Tobias J. (2000) Tolerance, withdrawal and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit (review). Critical Care Medicine 28(6), 2122-2132.
15. Whelan, K. T., Heckmann, M. K., Lincoln, P. A., & Hamilton, S. M. (2015). Pediatric withdrawal identification and management. Journal of Pediatric Intensive Care, 4(02), 073-078.
16. Fife, PharmD, A., Postier, MPH, A., Flood, PhD, A. & Friedrichsdorf, MD, FAAP, S. J. Methadone conversion in infants and children: Retrospective cohort study of 199 pediatric inpatients. Journal of Opioid Management 12, 123 (2016).