

# Opioid tapering and weaning protocols in pediatric critical care units: a systematic review

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## SUMMARY

**OBJECTIVE:** Opioid abstinence syndrome is common in the pediatric intensive care environment because sedation is often needed during the children's treatment. There is no specific guideline regarding the management of these patients; and lately, methadone is an important drug for the prevention of abstinence symptoms during the weaning of opioids. This study gathers the available research to establish the initial dose of methadone, the rate of taper and tools to recognize this syndrome and act promptly.

**METHODS:** A systematic review was made from data of four different databases. Forty-nine articles of observational and experimental studies were selected based on the inclusion criteria (critical pediatric patients in acute use of opioids) and exclusion criteria (previous chronic use of opioids, other medications). The data regarding specific themes were separated in sections: initial dose of methadone, use of protocols in clinical practice, abstinence scales and adjuvant drugs.

**RESULTS:** The articles showed a great heterogeneity of ways to calculate the initial dose of methadone. The pediatric intensive care units of the study had different weaning protocols, with a lower incidence of abstinence when a pre-defined sequence of tapering was used. The Withdrawal Assessment Tool - 1 was the most used scale for tapering the opioids, with good sensitivity and specificity for signs and symptoms.

**CONCLUSION:** There is still little evidence of other medications that can help prevent the abstinence syndrome of opioids. This study tries to promote a better practice during opioid weaning.

**KEYWORDS:** Review. Critical Care. Analgesics, Opioid. Child. Substance Withdrawal Syndrome.

## INTRODUCTION

Pediatric intensive care includes situations of physiological stress and emotional distress, like invasive procedures (arterial and venous catheterization, orotracheal intubation), care of skin lesions, and others. The child is susceptible to a low degree of cooperation and physical and mental suffering in this environment. Due to these reasons, the use of

analgesics and sedatives is an important concern in the care of critically ill children<sup>1</sup>.

The main agents used include opioids and benzodiazepines, drugs that on a prolonged use can have serious consequences for the patient, such as muscular atrophy, delirium, and abstinence<sup>1,2</sup>.

The prolonged use of sedatives can also cause tol-

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erance, which can be defined as the decrease of the drug's efficiency over time or the need of greater doses to achieve the same effect, a physiologic dependence which is how the body responds needing the maintenance of a certain agent to avoid the development of withdrawal<sup>3</sup>.

Abstinence Syndrome (AS) can be described as symptoms and signs associated with the process of discontinuing analgesics and sedatives, characterized by agitation, gastrointestinal and autonomic dysfunction. In this context, the development of strategies and drugs that can improve these collateral effects is of particular interest of the critical care physician<sup>2,3</sup>.

Protocols guiding the use of opioids and benzodiazepine are a form of standardizing the clinical practice by providing tools to identify signs and symptoms of tolerance, dependence, and withdrawal<sup>4,5</sup>, allowing for prompt action to minimize the physiological impact of the administration of sedatives in adequate doses and taper them safely.

Our group performed a Systematic Review of the medical literature in search for the best available evidence on methadone use for opioid weaning as a way to improve patient care in the pediatric intensive care setting. Our main focus was on the initial methadone dose used for the weaning process, the importance of weaning protocols and well-established dosage tapering schemes.

## METHODS

### Searching Criteria:

Two independent researchers performed a literature search on electronic databases (PubMed, EMBASE, SCOPUS, Web of Science) on July 2016. No time period restriction was applied. The terms used for research were: "substance withdrawal syndrome", "withdrawal syndrome", "opioid", "infant", "child", "adolescent", "pediatric", "critically ill". References cited on the selected studies were also searched for additional articles for potential inclusion.

### Inclusion and Exclusion Criteria:

Of the publications found on the search described above were included for the review the ones that fulfilled the following inclusion criteria: studies performed on critically ill pediatric patients (1 month to 18 years old) and admitted in intensive care units. All articles focused on the chronic use of opioids and

other drugs or published in languages other than English, Spanish and Portuguese were excluded.

### Analysis of included Studies:

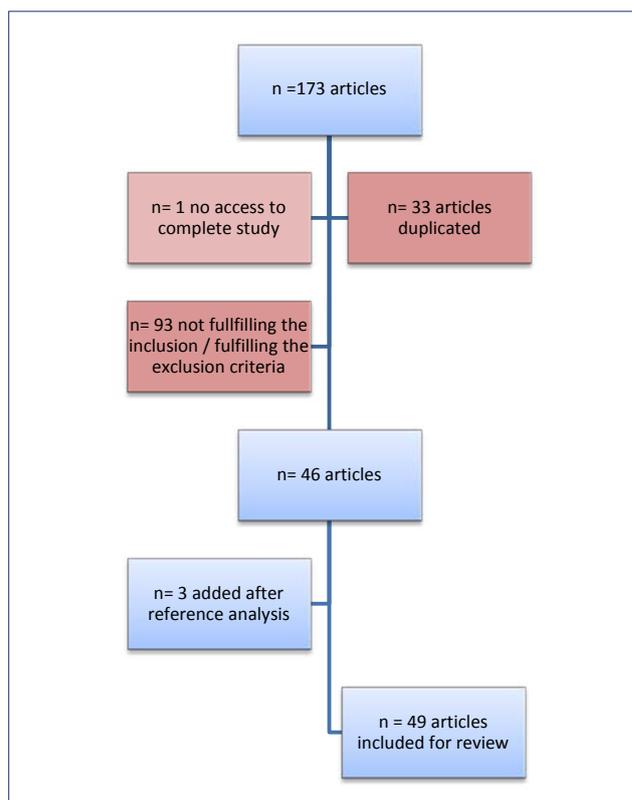
All studies that fulfilled the criteria above were reviewed by 2 independent researchers. After allocation on specific categories, the studies were qualitatively classified by the Jadad and Newcastle-Ottawa scales for their level of evidence<sup>6,7</sup>. A recommendation level for the proposed practice was issued based on the evidence available.

## RESULTS

### Study Selection

A total of 173 studies were selected after the database search. Of these, 33 were excluded after duplication removal, and 1 for lack of access to the complete article. Of the 139 remaining studies, after an analysis of inclusion and exclusion criteria, 46 articles remained for the review. After an in-depth analysis of the references of the included studies, another 3 articles were selected on an ancestry approach (Figure 1).

FIGURE 1: STUDY SEARCH AND SELECTION OF ARTICLES



The 49 studies included were heterogeneous on their study categories and study objectives (a total of 2 systematic reviews, 10 narrative reviews, 10 clinical trials, 5 cohorts, 7 case-control studies, 7 longitudinal studies, and 8 case-reports/case-series).

The included articles were divided by the 2 independent researchers into categories, based on their study focus: initial methadone dosage, opioid weaning protocol, abstinence scales, and adjuvant therapies.

### Initial Methadone Dosage

Of the 49 selected articles, 10 addressed the topic of the initial dose of methadone used for abstinence treatment and prevention. A total of 7 of them were included for systematic analysis: 2 clinical trials, 3 cohorts, 2 case-control studies. Three studies were

excluded due to the low level of evidence and references to a previously included study protocol.

Table 1 below shows the analysis of the results of all the studies included in this category:

The studies included analyzed different ways to determine the initial dosage of methadone used for opioid tapering. In spite of the great heterogeneity of the dose determination methods, a tendency to the use of low doses of methadone in the initial abstinence prevention therapy can be observed with no statistically significant differences in the incidence of abstinence symptoms or other outcomes. In this way, after systematic analysis, the use of low methadone initial doses (0,1 mg/kg/dose q6h) can be recommended (Grade B).

**TABLE 1.** STUDIES REGARDING INITIAL METHADONE DOSE. INCLUSION CRITERIA: USE OF CONTINUOUS FENTANYL OR MORPHINE FOR AT LEAST 5 DAYS AND/OR USE OF METHADONE DURING OPIOID TAPER. EXCLUSION CRITERIA: CNS ABNORMALITIES THAT INFLUENCED THE INTERPRETATION OF THE SIGNS AND SYMPTOMS RELATED TO THE OPIOID WITHDRAWAL SYNDROME.

Author	Study design (evidence)	Population	Initial dose	Withdrawal	Outcomes	Example (weight: 10kg, fentanyl 10mcg/h)
Bowens et al. (8)	Prospective Randomized Trial (IB)	n=78, 1-36 mo	"low-dose" (0,1mg/kg/dose) n=34 vs "high-dose" [0,1mg/kg/dose x recent fentanyl (mcg/kg/h)] n=26	No difference of incidence between the groups	No significant difference of oversedation incidence. Patients that failed to complete the assigned taper (18/78) had longer PICU length of stay and more days of ventilation	Methadone dose: 1mg
Lugo et al. (9)	Retrospective (III)	n=22, 6,1 ± 5,4 yrs	0,5 ± 0,22 mg/kg/dia q6h. Group (1) n=15 no need of dose increase; Group (2) n=7 dose was increased to 0,91 ± 0,37 mg/kg/dia	There was no withdrawal	No significant difference regarding the duration of taper	Methadone dose: 1,25mg
Johnson et al. (10)	Retrospective (III)	n=55, 0,03-12,2 yrs	initial "low-dose" <0,84mg/kg/dia n=27 vs initial "high-dose" ≥ 0,84mg/kg/dia n=28	No difference of incidence between the groups	No significant difference regarding length of stay in PICU	Methadone dose: 2,1mg
Siddappa et al. (11)	Retrospective (III)	n=30, 0,1 - 16,2 yrs	methadone (mg) = 3 x daily fentanyl dose (mg)	There was a significant difference of withdrawal incidence: 78% (7/9) of those who used ≤ 80% of the initial dose had symptoms in comparison with 14% (3/21) of the patients with the initial dose of >80%		Methadone dose: 0,72mg
Jeffries et al. (12)	Retrospective (III)	n=43, 0,25-201 mo	methadone (mg) = morphine (mg)	42% had withdrawal symptoms		
Meyer et al. (13)	Prospective (III)	n=29, 1 day - 19,8 yrs	enteral methadone (mg) = morphine IV (mg) x 2 = fentanyl (mcg/h) x 120	14% (4/29) had withdrawal symptoms		Methadone dose: 1,2mg
Robertson et al. (14)	Prospective comparison of protocol vs control groups (III)	n=20, 6 mo - 18 yrs	enteral methadone (mg) = morphine (mg) = daily fentanyl (mcg) x 10	No difference of incidence between the groups (protocol vs control)		Methadone dose: 2,4mg

## Tapering Protocols

Of the 49 selected articles, 5 addressed the topic of the opioid tapering protocol. Were included: 3 clinical trials, 2 cohort/case-control articles that studied the use of a pre-established protocol to guide methadone dose reduction and abstinence prophylaxis and treatment.

Table 2 below summarizes the results of the included studies in this category:

Berens et al.<sup>15</sup> compared two groups with previous use of opioids ≥ 5 days in relation to their time to methadone tapering (5 days x 10 days), with no statistically significant differences between the two approaches in relation to abstinence incidence and

**TABLE 2.** STUDIES REGARDING METHADONE WEANING PROTOCOLS. INCLUSION CRITERIA: USE OF CONTINUOUS FENTANYL OR MORPHINE FOR AT LEAST 5 DAYS AND/OR USE OF METHADONE DURING OPIOID TAPER. EXCLUSION CRITERIA: CNS ABNORMALITIES THAT INFLUENCED THE INTERPRETATION OF THE SIGNS AND SYMPTOMS RELATED TO THE OPIOID WITHDRAWAL SYNDROME.

Author	Study (evidence)	Population	Protocol	Rescue	Abstinence score	Groups	Incidence of abstinence	Secondary outcomes
Berens et al. (15)	Clinical trial (IB)	n=37, ≤ 18 yrs	Switch over fentanyl or morphine to enteral methadone using an initial dosage ("attack dosage") and a maintenance daily dosage. Comparison between 5 day weaning protocol reducing 20% of initial dosage + 5 days of placebo vs. 10 days weaning protocol reducing 10% of initial dosage.	Additional dose of methadone equal to the same dose administered the day before or 0,025mg/kg of morphine IV or 0,05mg/kg of methadone incrementally every 30 minutes	Neonatal Abstinence Score - Finnegan (NAS), modified Ramsay.	5 days (n=16) vs. 10 days (n=21)	No difference in incidence of abstinence between groups.	Duration of mechanical ventilation, vasopressor therapy, pediatric intensive care unit (ICU) length of stay and pediatric risk of mortality scores did not differ between the two groups
Steineck et al. (16)	Case - control (III)	n=52, 1m - 16 yrs	Weaning protocol based on the risk of development of abstinence by the duration of opioid and by the accumulate dose of fentanyl. Initial dose ranges from 0,05 to 0,2mg/kg/dose every 8 or 6 hours with reduction rate of 10% to 33% per day.	Additional dose of 0,05mg/kg of morphine IV every 2 hours if abstinence score between 9-11 or 0,1mg/kg if score ≥ 12	Modified Neonatal Abstinence Score - Finnegan (NAS)	pharmaceutical guided protocol (n=20) vs. regular protocol (n=32)	No difference in incidence of abstinence between groups.	A shorter weaning time of methadone (24,7 days vs. 15 days; p=0,003) and shorter length of hospital stay (38%) in the intervention group
Neunhoeffer et al. (4)	Clinical trial (IIB)	n=337, 0-18 yrs	Taper based on duration of opioid exposure: < 5 day - decrease of 50% of initial dose every 24hours; > 5 days - decrease of 10 to 20% every 24hours.	Dose of morphine, fentanyl and midazolam is adjusted according to COMFOT-B and NISS scale. The reduction is suspended for 24 hours if SOS ≥ 4	COMFORT-B, Nurse Interpretation Sedation Scale (NISS), Sophia Observation Withdrawal (SOS).	before protocol (n=165) vs. after protocol (n=172)	Lower incidence of abstinence after implementation of protocol (12,8% vs. 23,6%, p=0,005)	No difference in duration of mechanical ventilation, in days in ICU or total dosage of opioid.
Best et al. (17)	Prospective cohort (III)	n=145, 2 wks - 17 yrs	Group comparisons were made between patients with an intermittent weaning pattern, defined as a 20% or greater increase in daily opioid dose after the start of weaning, and the remaining patients defined as having a steady weaning pattern.	Not specified in the study	FLACC, Wong-Baker Faces, numerical scales to evaluate analgesia; State Behavior Scale; WAT-1.	intermittent pattern (n=66) vs. steady pattern (n=79)	Lower incidence of abstinence (WAT-1 ≥ 3) in the steady group: 46% vs. 85%, p<0,001. The tapering time of steady group was also shorter.	Comparison between protocol group and non-protocol group: lower length of mechanical ventilation (5,9 vs. 9,1 days, p<0,001), lower length of ICU stay (9,3 days vs. 12,8 days, p<0,001) and lower length of hospital stay (14 days vs. 21,5 days, p<0,001).
Robertson et al. (14)	Clinical trial (III)	n=20, 6 m - 18 yrs	Weaning protocol based on duration of opioid exposure: 7 to 14 days: decrease of 20% every day (taper time of 5 days) > 14 day: decrease of 20% every 2 days (taper time of 10 days)	Not specified in the study	Scale based on signs and symptoms from Neonatal Abstinence Score.	protocol (n=10) vs. non protocol (n=10)	No difference in incidence of abstinence between groups.	Lower weaning time in protocol group (9 days vs. 20 days, p<0,001).

ICU length-of-stay showing that a reduction of 20% or 10% of the initial dose had similar results. On the other hand, Steineck et al.<sup>16</sup> compared tapering based on a protocol-based approach with usual care, with no difference on the incidence of abstinence, but with a statistically significant reduction on methadone tapering time and hospital length-of-stay. In this study the transition of intravenous (IV) opioids to enteral was made in 24 to 48 hours, and the doses were decreased daily depending on the previous duration of the IV treatment (< 5 days: q8h to q12h to q24h to suspension; ≥ 5 days: 20% to 10% of initial dose q6h and after q8h to q12h to q24h to suspension).

Neunhoffer et al.<sup>4</sup> compared two periods (before and after the implementation of an abstinence control protocol), showing a reduction in the incidence of abstinence (12,8% x 23,6%;  $p = 0,005$ ) with no difference in the hospital length-of-stay. The same approach was performed by two other groups (18), performing analysis on a population before and after the implementation of an abstinence management protocol, showing reductions in the methadone tapering time and hospital length-of-stay.

The evidence points towards safe and fast daily weaning protocols especially in those patients with shorter use of opioids ( $\leq 5$  days) without the increase of abstinence symptoms<sup>15,16,19</sup>.

Despite the differences in the protocols implemented on the different studies, the systematical approach to the monitoring of abstinence symptoms and the adjustment of methadone dosage, as well as reduction schemes, can be helpful in the management of opioid withdrawal. Based on the studies above, we can recommend the use of abstinence management protocols, based on the use of assessment scales and pre-defined methadone dose tapering; the weaning rates cannot yet be specified by the available data (Grade: B).

### Abstinence Evaluation Scales and Adjuvant Therapies:

Due to the low level of evidence of the studies evaluated, the same systematic approach applied above was not possible. In this way, it was decided to perform a narrative review on these two topics, in a way to provide some basis for these practices. Of the searched articles, 31 analyzed aspects of symptom evaluation and/or adjuvant therapies.

### Abstinence Scales (Narrative Review):

The three main scores will be briefly presented below:

Finnegan's neonatal abstinence score: the first widely used abstinence scale in the pediatric setting was developed based on the observation of neonates exposed to opioids during gestation (20). It is composed of 21 evaluation items of neurological, gastrointestinal and autonomic symptoms, generating a numeric score, on which a pharmacologic intervention is warranted on values  $\geq 8$  (21). Its main limitation is the lack of validity outside neonatal period<sup>21</sup>.

Sophia observational withdrawal symptoms scale (SOS): The SOS is composed of 15 items, including vital signs, gastrointestinal, neurologic and autonomic symptoms. The score was developed through a prospective observational study on 76 intensive care patients under 16 years-old who received at least 5 days of continuous sedation (fentanyl, midazolam or morphine)<sup>22</sup>. The lack of multicenter validation is considered the main limitation of SOS<sup>23</sup>.

Withdrawal Assessment Tool-1 (WAT-1): Constitutes the most widely used abstinence evaluation tool in a pediatric intensive care setting, because of its easier bedside application, composed of 11 items (including gastrointestinal, neurologic and autonomic symptoms) (24). It was validated on a subsequent multicenter, presenting a sensibility of 87.2% and specificity of 88%, for values  $\geq 3$  (25).

Although the impossibility of performing a proper systematic recommendation, it was clear to our group that the better external validity and systematic approach on the confederation favor the use of WAT-1 as an abstinence assessment tool in a pediatric intensive care setting. However, more evidence is needed to establish the best assessment method.

### Adjuvant Therapies (Narrative Review):

We found 5 case-reports/series-of-cases describing the adjuvant use of dexmedetomidine<sup>26-28</sup>, naloxone and clonidine<sup>29</sup>, oral morphine<sup>30</sup> and one retrospective study ( $n = 9$ ) that analyzed the efficacy of subcutaneous fentanyl<sup>31</sup>, on the management of abstinence after prolonged use of opioids. All the reports were about specific populations, such as post-cardiac surgery subjects (27,28), which makes external validity an issue. The small population of patients exposed to these interventions makes it impossible to issue a recommendation on the use of any of

these adjuvant therapies, which makes more studies necessary to assess the potential of some of these interventions.

## DISCUSSION/CONCLUSION

The use of opioids is well-established in the critical care setting with the goal of analgesia and sedation, reducing stress and distress of the pediatric patient<sup>1,3,32</sup>. The prolonged use of these agents has the potential to lead to abstinence<sup>33-35</sup>, a clinical syndrome that can increase the length-of-stay and decrease ventilation-free day of patients, culminating with worst prognosis<sup>2,8</sup>.

Our systematic review tries to give emphasis to this growing issue and to promote better scientific-based practices for the management and prevention of abstinence. In spite of the poor level of evidence and lack of substantial and well-controlled trials, some observations could be made.

The use of protocols of opioid tapering and pharmacological management had a tendency of reduction of the total duration of methadone tapering and hospital length-of-stay<sup>4,14-17,36</sup>. The most systematic and objective approach favored a quicker reduction of the daily doses of methadone, promoting a shorter time to its discontinuation, in spite of the great variability of the implemented schemes. More research is needed to further support this observation, especially through clinical trials or prospective observational studies, preferably in a multicenter setting.

The initial dose of methadone is still a big issue, with different ways of calculating and determining it leading to either low or high doses (above 0.1 mg/

kg q6h)<sup>(8-14)</sup>. Although there is not a consensus on the topic, and the results of the papers presented above having showed no statistical differences, the use of low methadone doses can be recommended based on the theoretical benefit of less potential adverse reactions<sup>9-12,37,38</sup> more commonly associated to higher doses of opioids. Nevertheless, this observation regarding adverse reaction is not supported by the articles included in our systematic analysis. A recent meta-analysis and systematic review by Derivan et al.<sup>39</sup> showed that initial doses are widely variable throughout the medical literature, ranging from 1 to 17-times the previously used doses of fentanyl through opioid equivalence.

Monitoring signs and symptoms of abstinence can be made by a wide arsenal of scales and tools, varying from service to service, depending on its clinical routine<sup>40</sup>. There is still a gap of knowledge with good control and systematically designed to assess this question. In light of such a lack of evidence on medical literature, WAT-1 appears to be the most promising and best-defined evaluation tool<sup>24,25</sup>, leading to its recommendation and implementation on many pediatric intensive care units. However, there is still a promising field for further research on the topic, especially comparatively analyzing the different methods of evaluation.

Adjuvant therapies, such as the use of dexmedetomidine<sup>28</sup>, show promising impressions. However, the great variability of the study population and the small number of patients on which they were tested<sup>26-29</sup> make the external validity an issue, making it crucial to further investigate it using a bigger population and on a more controlled approach.

## RESUMO

**OBJETIVO:** A síndrome de abstinência de opioides é comum no ambiente de terapia intensiva pediátrica porque a sedação é frequentemente necessária durante o tratamento das crianças. Não existe uma diretriz específica sobre o manejo desse paciente e, ultimamente, a metadona tem sido uma droga importante para a prevenção dos sintomas de abstinência durante o desmame dos opioides. Este estudo reúne as pesquisas disponíveis para estabelecer a dose inicial de metadona, taxa de redução e ferramentas para reconhecer essa síndrome e agir prontamente.

**MÉTODOS:** Uma revisão sistemática foi feita a partir de dados de quatro diferentes bases de dados. Quarenta e nove artigos, de estudos observacionais e experimentais, foram selecionados com base nos critérios de inclusão (pacientes críticos pediátricos em uso de opioides agudamente) e critérios de exclusão (uso crônico prévio de opioides, outros medicamentos). Os dados referentes a temas específicos foram separados em seções: dose inicial de metadona, uso de protocolos na prática clínica, escalas de abstinência e drogas adjuvantes.

**RESULTADOS:** Os artigos mostraram uma grande heterogeneidade de formas de calcular a dose inicial de metadona. As unidades de terapia intensiva pediátrica do estudo apresentaram diferentes protocolos de desmame, com menor incidência de abstinência quando foi utilizada uma sequência predefinida de redução gradual. A Ferramenta de Avaliação de Retirada - 1 foi a escala mais utilizada durante a redução dos opioides, com boa sensibilidade e especificidade para sinais e sintomas.

**CONCLUSÃO:** Ainda há poucas evidências de outros medicamentos que possam ajudar a prevenir a síndrome de abstinência dos opioides. Este estudo tenta promover uma prática melhor durante o desmame dos opioides.

**PALAVRAS-CHAVE:** Revisão. Cuidados críticos. Analgésicos opioides. Criança. Síndrome de Abstinência a Substâncias.

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