Medicine®

Assessment and treatment of the withdrawal syndrome in paediatric intensive care units
Systematic review

Jennihe Alejandra Ávila-Alzate[a], Juan Gómez-Salgado[b,c,*], Macarena Romero-Martín[d], Santiago Martínez-Isasi[e], Yolanda Navarro-Abal[f], Daniel Fernández-García[g]

Abstract

Background: Sedoanalgesia secondary iatrogenic withdrawal syndrome (IWS) in paediatric intensive units is frequent and its assessment is complex. Therapies are heterogeneous, and there is currently no gold standard method for diagnosis. In addition, the assessment scales validated in children are scarce. This paper aims to identify and describe both the paediatric diagnostic and assessment tools for the IWS and the treatments for the IWS in critically ill paediatric patients.

Methods: A systematic review was conducted according to the PRISMA guidelines. This review included descriptive and observational studies published since 2000 that analyzed paediatric scales for the evaluation of the iatrogenic withdrawal syndrome and its treatments. The eligibility criteria included neonates, newborns, infants, pre-schoolers, and adolescents, up to age 18, who were admitted to the paediatric intensive care units with continuous infusion of hypnotics and/or opioid analgesics, and who presented signs or symptoms of deprivation related to withdrawal and prolonged infusion of sedoanalgesia.

Results: Three assessment scales were identified: Withdrawal Assessment Tool-1, Sophia Observation Withdrawal Symptoms, and Opioid and Benzodiazepine Withdrawal Score. Dexmedetomidine, methadone and clonidine were revealed as options for the treatment and prevention of the iatrogenic withdrawal syndrome. Finally, the use of phenobarbital suppressed symptoms of deprivation that are resistant to other drugs.

Conclusions: The reviewed scales facilitate the assessment of the iatrogenic withdrawal syndrome and have a high diagnostic quality. However, its clinical use is very rare. The treatments identified in this review prevent and effectively treat this syndrome. The use of validated iatrogenic withdrawal syndrome assessment scales in paediatrics clinical practice facilitates assessment, have a high diagnostic quality, and should be encouraged, also ensuring nurses' training in their usage.

Abbreviations: APD = acute pulmonary disease, BSS = Behavioural State Scale, BT = bacterial tracheitis, BZD = benzodiazepines, CASPe = Critical Appraisal Skills Programme España, CENTRAL = Cochrane Central Register of Controlled Trials. CINAHL = Cumulative Index to Nursing & Allied Health Literature, CNS = central nervous system, DBP = diastolic blood pressure, DXD = dexmedetomidine, DZM = diazepam, ECMO = extracorporeal oxygenation membrane, FNT = fentanyl, GA = gestational Age, GI = gastrointestinal, HI = head injury, HR = heart Rate, ICI = Interclass Correlation Index, IQR = interquartile range, IVR = intravenous route, IWS = Iatrogenic Withdrawal Syndrome, LILACS = Latin American and Caribbean Literature in Health Sciences, LR = likehood ratio, LRZ = lorazepam, MDZ = midazolam, MeSH = Medical Subject Headings, MV = mechanical ventilation, NMB = neuromuscular blockers, NRS = Numerical Rating Scale, NWS = Neonatal Withdrawal Score, OBWS = Opioid and Benzodiazepine Withdrawal Score, OR = oral route, PB = phenobarbital, PH = pulmonary haemorrhage, PHT = pulmonary hypertension, PICU = Paediatric Intensive Care Units, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PWI = Paediatric Withdrawal Inventory, RMF= Remifentanil, ROC = receiver operating characteristic, RR = respiratory rate, SBP = systolic blood

[a] Department of Nursing, University of Valencia, Valencia, [b] Department of Sociology, Social Work and Public Health, University School of Social Work, Huelva, [c] Safety and Health Postgraduate Programme, Universidad Espíritu Santo, Guayaquil, Ecuador, [d] Centro Universitario de Enfermería Cruz Roja, University of Sevilla, Sevilla, [e] CLINURSID Research Group, Nursing Department, University of Santiago de Compostela, Santiago de Compostela, Galicia, [f] Department of Social, Developmental and Education Psychology, University of Huelva, [g] University Hospital of León, León, Spain.

* Correspondence: Juan Gómez-Salgado, University School of Social Work. Campus del Carmen, Universidad de Huelva, Avenida de las Fuerzas Armadas, S/N, Huelva 21007, Spain (e-mail: jgsalgad@gmail.com).

1. Introduction

In paediatric intensive care units (PICU), sedoanalgesia is an essential part of the treatment of critical patients. Some of its main objectives consist in avoiding stress and other negative psychological effects, as well as the physical suffering related to invasive procedures, preventing accidental removal of vascular catheters and self-extubation, and encouraging the adaptation of the patient to mechanical ventilation (MV).[1,2] However, it is difficult to achieve optimal sedation and analgesia in children. In fact, it is only achieved in 60% of patients.[1,3] That is why mismatches frequently occur in PICU regarding over or under sedoanalgesia alike. These phenomena are related to increased hospital stays, prolongation of MV, increased morbidity and mortality, inadequate management of pain, increased risk of nosocomial infections, and occurrence of iatrogenic syndrome, among others.[1–3]

There are few recommendations on the drugs that must be used for sedation and analgesia in the paediatric critical patient. In the clinical practice of PICUs, the most used pharmacological agents are opioids and benzodiazepines (BZD), being fentanyl (FNT) the analgesic of choice, followed by paracetamol and metamizole and, as sedative, midazolam (MDZ), followed by lorazepam, ketamine, and propofol.[3,4] The benefits of both pharmacological groups on the critical patient are evident, but they also generate tolerance and physical dependence, making higher doses and prolonged infusions necessary in order to maintain the desired effects and avoid the WS.[1,5]

The iatrogenic withdrawal syndrome (IWS) consists in the set of signs and symptoms that appear after removing or decreasing psychoactive drugs that have been administered for a long time or in high doses.[6] Its incidence in the PICU is highly variable. In Spain, it affects 50% of the patients who have a continuous infusion of sedoanalgesia for 48 hours, increasing to more than 80% when infusion lasts more than 5 days.[7] In other countries, the incidence of the IWS is similar, reaching 50% in patients with infusions of more than 24 hours of duration, and an increase from 80% to 100% when exceeding 5 days of treatment.[7–10] Regarding the IWS signs and symptoms, these vary depending on the drug and patient characteristics, such as age, cognitive status, etc. The most common manifestations are at breathing level (tachypnoea), gastrointestinal (nausea, vomiting, diarrhea), nervous system (sweating, tachycardia, mydriasis), and motor level (tremors, abnormal movements, hyperreflexivity, hypertonia).[1,8] In addition, it is worth noting that opioid abstinence originates more superficial movement disorders and gastrointestinal disorders, as opposed to the withdrawal of BZD.[11]

On the other hand, factors that are related to the appearance of the IWS include the use of hypnotics and analgesics, duration, and abrupt interruption of the sedoanalgesia, the patients' characteristics, and health care system factors.[1,12,13] Regarding the characteristics of the medications used in the treatment, it has been observed that the risk of IWS is higher when given synthetic and/or short half-life opioids. Similarly, other factors have been associated with an increased incidence of IWS, such as cumulative doses of hypnotics and opioids (MDZ $\geq$ 40–60 mg/kg FNT $\geq$ 0.48–1.5 mg/kg, sufentanil $\geq$95.61 µg/kg/hour and propofol $\geq$4 mg/kg/hour); continuous infusions of sedoanalgesia for a period longer than 3–5 days; simultaneous use of muscle relaxants; and sudden interruption of sedoanalgesia.[1,7–9] As for the characteristics of the patient, a relationship has been observed between the IWS, age, and clinical status of the patient. In children, the younger they are, the greater the vulnerability to IWS. However, the symptoms are more pronounced in term infants that in preterm infants.[14] Likewise, neurological conditions such as brain injury and ischemia and the presence of cognitive and functional decline are linked to an increased risk of IWS.[15] With respect to the health system factors, the absence of an interdisciplinary group, the lack of training and professional experience, the small number of sedation protocols, and the withdrawal of sedoanalgesia increase the incidence of IWS.[12]

The IWS is usually under diagnosed and undertreated, as its signs and symptoms often change and may be confused with other more frequent conditions in the paediatric critical patient. In fact, there is no gold standard for the diagnosis or assessment of the IWS by opioids and/or BZD.[1] The majority of studies on IWS carried out until now have used unvalidated scales for its evaluation in the paediatric population. Furthermore, most of the scales used in research and clinical practice employ tools specifically designed for newborns but that are also applied to the rest of paediatric patients, such as the Finnegan scale, the neonatal withdrawal index to narcotics, etc.[12] However, in recent years, new IWS diagnostic and monitoring instruments have been specifically designed and validated for infants and children of older ages. Therefore, the lack of knowledge on a validated IWS diagnostic and assessment scale in paediatric patients makes the evaluation of the effectiveness of treatments for this syndrome complex, and may even lead to wrong conclusions.[16] Recently, there have been studies that propose prevention strategies and treatments for the IWS, including the daily interruption of sedation, the gradual reduction of sedoanalgesia, a decrease in analgesics doses, the administration of alpha-2 agonists, or the transition to long half-life barbiturates, among others. However, the best treatment for the IWS in critical paediatric patients and the necessary conditions for its safe usage have not been established.[17]

The present work proposes a twofold objective: to identify and describe both the paediatric diagnostic and assessment tools for the IWS, and the treatments for the IWS in paediatric critical patients.

2. Materials and methods

A systematic review was carried out following the recommendations for systematic reviews collected in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18] The checklist and flow diagram are included as supplementary files (Fig. 1 and Supplementary File 1, http://links.lww.com/MD/D638).
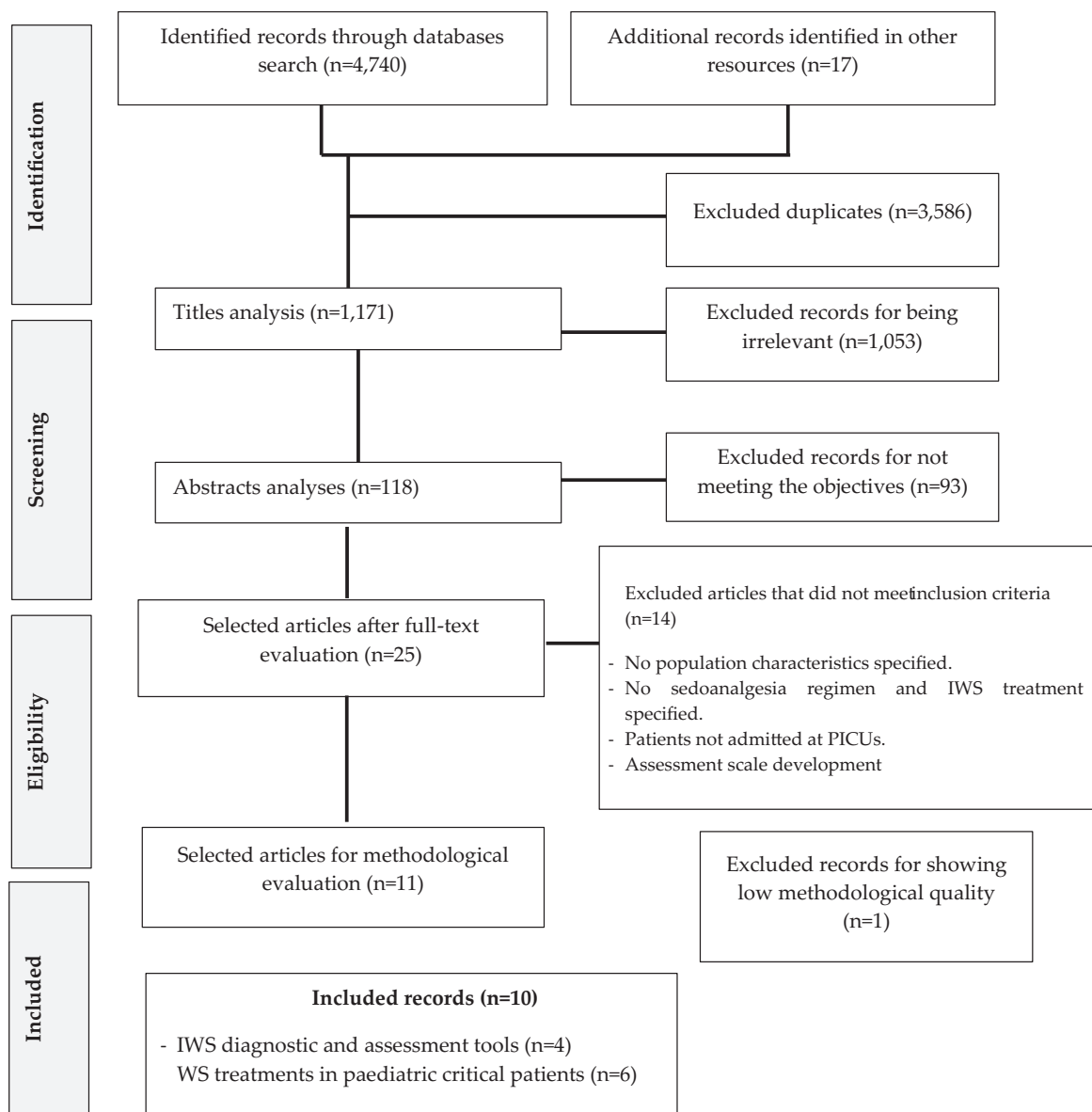
Figure 1. PRISMA flow chart of the study selection process.

2.1. Search strategy

An electronic search of articles was carried out during the months of February to April, 2018 in the following databases: Medline-PubMed, Embase-Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Literature in Health Sciences (LILACS, for its acronym in Spanish), Web of Science, CINAHL, Scopus, and Google Scholar.

The terms were found in the Medical Subject Headings (MeSH), in addition to free terms: Opioid; Benzodiazepines (MeSH); Hypnotics and Sedatives (MeSH); Iatrogenic Withdrawal Syndrome; Substance Withdrawal Syndrome (MeSH); Child*(MeSH); Pediatric intensive care units (MeSH); Treatment; Therapy (MeSH); Substance Withdrawal Syndrome (MeSH); Assessment tool; Scale. With these terms, along with the truncation characters (*) and Boolean AND and OR operators, the search strategies for each of the objectives of the review were built.

The following strategies were used for the search of IWS assessment and diagnostics scales: Substance Withdrawal Syndrome AND Assessment tool; Substance Withdrawal Syndrome AND scale AND child*; Substance Withdrawal Syndrome AND Assessment tool AND child*; Opioid AND Benzodiazepine AND Substance Withdrawal Syndrome AND Assessment tool; Hypnotics AND Sedatives AND Substance Withdrawal Syndrome AND Assessment tool; Iatrogenic Withdrawal Syndrome AND Assessment tool AND pediatric intensive care.

The following strategies were used for the IWS treatments search: Hypnotics AND Sedatives AND Iatrogenic Withdrawal Syndrome; Opioid AND Benzodiazepine AND (Iatrogenic Withdrawal Syndrome OR Substance Withdrawal Syndrome); Opioid AND Benzodiazepine AND Substance Withdrawal Syndrome AND Child*; Opioid OR benzodiazepine AND Substance Withdrawal Syndrome AND pediatric intensive care; Iatrogenic Withdrawal Syndrome AND Therapy; Iatrogenic

Ávila-Alzate et al. Medicine (2020) 99:5

Medicine

Withdrawal Syndrome AND Treatment AND Child*; Iatrogenic Withdrawal Syndrome OR Substance Withdrawal Syndrome) AND Therapy AND Child*.

Additionally, the references of relevant articles were reviewed to identify studies that met the objectives of the review and to include them in the screening process.

2.2. Selection criteria

The selected studies for the development of this systematic review met the following inclusion criteria:

- Types of studies: randomized clinical trials, observational and descriptive studies published in Spanish or English, available in full text. Due to the limited number of records on this subject, documents from 2000 to 2018 were included.
- Participants: Studies involving neonates, newborns, infants, pre-schoolers, and adolescents up to age 18 who were admitted to the PICU with continuous infusion of hypnotics and/or opioid analgesics and who presented signs or symptoms of deprivation related to withdrawal and prolonged infusion of sedoanalgesia.
- Intervention: Studies in which drugs were administered for the treatment or prophylaxis of the IWS, produced by continuous infusions of hypnotics and/or opioids such as α2-adrenergic agonists, buprenorphine, methadone, naloxone, and dexmedetomidine. In addition, studies that compared the efficacy of different drugs, dosages, and posology for the treatment or prevention of the IWS were selected. On the other hand, articles that estimated the validity, specificity and sensitivity of different diagnostic and evaluation instruments of the paediatric IWS were included. In addition, records that compared the effectiveness of these scales were selected.

Studies that met the following criteria were excluded:

- Researches involving participants with neonatal withdrawal syndrome (newborns to mothers with substance dependence or exposed to opiates and illicit drugs in utero), cognitive alterations, IWS due to drug abuse, IWS related to drugs other than hypnotics and/or opioids, and who were also admitted to non-critical care units.
- Publications that were oriented to the treatment or prophylaxis of tolerance to hypnotics and opiates.
- Studies that did not specify the administered treatment of IWS, nor the assessment methods or the diagnostic criteria for the IWS (cut-off score of a scale, number of manifestations of the IWS, severity of the symptoms, etc.).
- Articles analyzing assessment and/or diagnostic tools of neonatal IWS and delirium.

2.3. Selection of studies and data extraction

The studies selection was carried out in 3 phases. In the first phase, the titles of all the results were screened by a reviewer. Then, 2 reviewers read the summary of the articles selected in the previous phase, discarding irrelevant documents. The third phase consisted of the final selection of studies for the review, after the full text was read and the verification of compliance with the inclusion and exclusion criteria was carried out. In situations of disagreement, a consensus was reached between the 2 reviewers.

Once the final selection of articles for the review was made, the analytical reading, data extraction and classification of the

information was carried out in evidence tables that were specifically designed for this purpose. In these tables, the following items were extracted: first author, year of publication, design of the study, objectives, population, intervention, assessment method, main results, and conclusions.

2.4. Assessment of the methodological quality of the studies

The methodological quality of cohort studies was assessed through the Critical Appraisal Skills Programme España (CASPe) templates[19,20] in order to identify possible biases. Articles that obtained more than 6 points were included, considering as good quality scores those > 8, 6–8 as average quality, and ≤5 as low quality. Reports and case series were assessed with the CARE Guide.[21] Articles that fulfilled at least 80% of the items and contained all the sections of these types of studies were selected.

In situations of discordance, a critical analysis of the study was repeated, and discordance was resolved by mutual agreement.

2.5. Ethical considerations

Ethical considerations were identified in the reviewed articles, and no ethical issues were raised.

3. Results

A total of 4740 bibliographical references were initially identified by following the search strategy, and 17 additional records through the assessment of the references of the screened studies. 3586 duplicated items were removed.

In the first screening (title reading), 1053 studies were excluded. Subsequently, the analysis of summaries of 118 records was developed, eliminating 93 of them. Therefore, 25 articles were examined in full text, of which 11 met the inclusion criteria and underwent methodological assessment.[22–32] Finally, 10 studies were included in the review.[22–30,32] The degree of concordance between the 2 reviewers was determined with the Cohen Kappa index, which was 0.73 (confidence interval, CI 95%: 0.47–0.88). The studies selection process for the review developed according to PRISMA is reflected in Figure 1.

Regarding the type and design of the studies, 6 were observational and 4 were descriptive. The first 6 consisted of 4 prospective cohort studies and 2 case-control analyses. As for the descriptive records, there were 3 case reports and 1 case series.

3.1. Methodological quality

Of the observational studies, 1 did not report follow-up losses, originating a selection bias and affecting its validity.[30]

As for the descriptive articles, only 1 case report specified the study design in the title.[27] Although no study indicated whether the patient's informed consent was requested, all were approved by an ethics committee. On the other hand, 1 study represented the most relevant events in a table.[26] Finally, a case series was the only study that did not comply with at least 80% of the items included in the CARE Guide, and it was decided to exclude it from the review by mutual agreement between the reviewers.[31] The results of the methodological assessment are collected in Tables 1–3.

Ávila-Alzate et al. Medicine (2020) 99:5

www.md-journal.com

Table 1

Methodological assessment of observational cohort studies, according to the Critical Appraisal Skills Programme (CASP).

Criteria	Frank et al, 2012	Lugo et al, 2001	Frank et al, 2004	Frank et al, 2008
	A/Are the study results valid?			
1 Is the study focused on a clearly defined subject?	Yes	Yes	Yes	Yes
2 Was the cohort recruited in the most appropriate way?	Yes	Yes	Yes	Yes
3 Was the result measured in a precise way, so as to minimise possible biases?	Yes	Yes	Yes	Yes
4 Did the authors consider the potential effect of confounding factors in the design and/or analysis of the study?	Yes	Yes	Cannot say	Yes
5 Was the subjects' follow-up sufficiently complete and prolonged in time?	Yes	Yes	Yes	Yes
	B/ What are the results?			
6 What are the results of this study?	Higher accumulated doses of opioids (P = .004). Longer duration of treatment (P = .004) Longer time to withdrawal (P = ,008)	Fentanyl suspension in a mean of 2.6 days, when starting methadone 1.6 ± 1.9 days before reducing fentanyl.	Patients with morphine and fentanyl showed a higher frequency of IWS symptoms (P = .004). OBWS scale: Sensitivity 50% Specificity 87%.	WAT-1 scale with 11 items Maximum score 12 Sensitivity 87% Specificity 88% Cut-off score WAT-1 ≥3.
7 How precise were the results?	95%	95%	95%	95%
	C/ Are the results applicable to your setting?			
8 Do you consider the results believable?	Yes	Yes	Yes	Yes
9 Do these results coincide with other available evidence?	Yes	Yes	Yes	Cannot say
10 Can these results be applied to your setting?	Yes	Yes	Yes	Yes
11 Will this change your clinical decisions?	No	No	No	No

Table 2

Methodological assessment of observational studies, including cases and controls, according to the Critical Appraisal Skills Programme (CASP).

Criteria	Siddappaet al, 2003	Lardieri et al, 2015
A/ Are the study results valid??		
1 Is the study focused on a clearly defined subject?	Yes	Yes
2 Did the authors choose an appropriate method to answer the question?	Yes	Yes
3 Were the cases recruited/included in an acceptable way?	Yes	Yes
4 Were controls selected in an acceptable way?	Yes	Yes
5 Was the exposition measured in a precise way so as to minimise possible biases?	Cannot say	Cannot say
6A Which confounding factors did the authors consider?	Infusion of muscle relaxants. Medication with opioids other than FNT Previous accumulated doses of benzodiazepines. Admitted patients from other hospitals	Duration of clonidine treatment. Extra doses of opioids. Simultaneous medication with other drugs during sedoanalgesia withdrawal. Previous interventions due to base disease (ECMO).
6B Did the authors consider the potential effect of confounding factors in the design and/or analysis of the study?	Yes	Yes
7 What are the results of this study?	80% of methadone recommended dose (2.4 times that of fentanyl per day), seems effective in preventing the WS. Ten patients did not present or show minimum symptoms of withdrawal. On the other hand, twenty subjects showed significative withdrawal symptoms.	Patients treated with clonidine showed lower WAT-1 mean scores (0.8 vs 3.2 [p=0.49]) and experimented less tachycardia (112 bpm vs 138.4 bpm [p=0.03]) than those without clonidine treatment. No significant differences were found between both groups regarding blood pressure before and after dexmedetomidine suspension [p=0.624; p=0.851].
B/ What are the results?		
8 How precise are the results? How precise is risk assessment?	95%	95%
9 Do you believe these results?	Yes	Yes
C/ Are the results applicable to your setting?		
10 Can these results be applied to your setting?	Yes	Yes
11 Do these results coincide with other available evidence?	Yes	Cannot say

Ávila-Alzate et al. Medicine (2020) 99:5

Medicine

Table 3

Methodological assessment of case report studies, according to the CARE Guide.

CARE check list (2013)			Cho et al, 2007	Weber et al, 2013	Finkel et al, 2005	Tobias et al, 2006
Subject		Description of check list item		Page		
Title	1	The words "case report" must appear in the title, along with the topic of interest in each case	173	–	–	–
Key words	2	Key elements of the case in 2 to 5 key words	173	62	–	201
Summary	3a	Introduction What is unique in this case? What does it add to the scientific literature?	173	62	2110	201
	3b	Main symptoms of the patient and relevant clinical outcomes	173	63	2110–11	201
	3c	Main diagnoses, therapeutic interventions and outcomes	–	63	2110–11	201
	3d	Conclusion: What are the main reasons to carry out the case?	173	–	2110	201
Introduction	4	A brief summary of this cases' antecedents that refers to the clinical literature available	173	63	2110–11	201
Patient data	5a	Demographic information (age, sex, ethnic origin, occupation)	173	63	2110–11	201
	5b	Main symptoms of the patient (main complains)	174	63	2110–11	–
	5c	Physician, family and psychosocial record, including comorbidities, as well as relevant genetic information	173	63	2110–11	–
	5d	Relevant previous interventions and their outcomes	173	63	2110–11	–
Clinical findings	6	Describing physical exploration (PE) and relevant findings	173	63	2110–11	–
Chronology	7	Representing relevant occurrences related to their diagnosis and interventions (table or figure)	–	64	–	–
Diagnostic assessment	8a	Diagnostic method (such as PE, lab tests, images, questionnaires)	173	64	2110–11	202
	8b	Diagnosis challenges (such as economic, language, or cultural)	–	–	–	–
	8c	Diagnosis reasoning that includes other considered diagnoses	173	63	2110–11	202
	8d	Prognostic characteristics (such as start-up in oncology). Where it was applied in each case.	–	–	–	–
Therapeutic intervention	9a	Types of intervention (such as pharmacological, surgical, preventive self-care)	174	63	2110–11	202
	9b	Administration of the intervention (such as doses, resistance, duration)	174	63	2110–11	202
	9c	Changes in the intervention (justified)	174	63	2110–11	202
Follow-up and results	10a	Outcomes assessed by the physician and, in its case, by the patient	174	63	2110, 2111	202
	10b	Results of relevant follow-up test	174	63	2110–11	202
	10c	Adherence and tolerance to the intervention (How was the assessment performed?)	174	63	2110, 2111	202
	10d	Adverse or unexpected events	174	63	2110–11	202
Discussion	11a	Discussion of strengths and limitations in the management of the case	175–6	64	2111, 2112	204
	11b	Discussion of pertinent clinical literature	175–6	64,65	2111, 2112	203–204
	11c	Conclusions justification (including assessment of possible causes)	175–76	64,65	2112	204
	11d	Main reasons to carry out the case report	176	65	2111	204
Patient's perspective	12	Did the patient share his/her perspective or experience? (Include when appropriate)	–	–	–	–
Informed consent	13	Did the patient give his/her informed consent? Indicate if it was requested	No	No	No	No

3.2. IWS assessment instruments

Four observational articles focused on the analysis of IWS assessment scales related to opioids and sedatives in critically ill children.[22,23,25,32] All of them were prospective cohort studies, involving 378 patients and performing 6323 IWS tests. Two of them examined the Withdrawal Assessment Tool-1 (WAT-1) scale[22,23]; another one analyzed the Opioid and Benzodiazepine Withdrawal Score (OBWS)[32]; and finally, 1 study assessed the Sophia Observation Withdrawal Symptoms (SOS).[25] Table 4 describes the studies that analyze the IWS assessment tools included in this review.

Three validated IWS assessment scales, specific for the paediatric population, were identified: WAT-1, SOS, and OBWS.[22,23,25,32] As for the structure, the OBWS complies with 21 items that estimate the frequency and severity of withdrawal symptoms.[32] The WAT-1 is constituted by 11 items and it values the presence and severity of the manifestations of

Table 4

Description of the studies on IWS assessment tools included in the review.

Author (year)	Design	Objectives	Population (age)	Assessment method	Comparison	Main outcomes	Conclusions
Ista et al, 2013	Prospective uni-centre study of repeated measures	Establishing the SOS scale cut-off point and prove its sensibility and specificity	N = 154 children (mean: 5 months) Inclusion: Patients ≤16 years, with BZD infusion and/or opioids ≥ 5 days. Exclusion: Epileptic status treated with MDZ or BNM, subjacent neurological disease subjacent.	Scale: SOS From 48h sedoanalgesia post-suspension or 28 days after the start of withdrawal. Measurement: 3 times a day and in the event of IWS symptoms.	NRS- Withdrawal	Cut-off score: ≥4 Sensitivity: 83% Specificity: 93%.	SOS is a valid scale with good psychometric properties to assess IWS symptoms in PICU patients.
Frank et al, 2004	Prospective uni-centre study with repeated measure	Estimating: IWS symptoms occurrence with opioids and BDZ withdrawal protocol. OBWS validity.	N = 15 children (6 weeks-28 months) Inclusion: Patients opioids and BDZ infusion ≥4 days. Exclusion: Documented brain injuries and convulsions.	Scale: OBWS Measurement every 4h, up to 2 days after sedoanalgesia suspension.	Nurses' clinical judgement (presence or absence of withdrawal symptoms)	Cut-off score: ≥8 Sensitivity: 50% Specificity: 87%	OBWS validity was appropriate for its clinical application but must be improved.
Frank et al, 2008	Prospective multi-centre study of repeated measures	Developing an IWS assessment scale and evaluate its validity.	N = 83 children (7 months-10 years) Inclusion: Patients from 2 weeks to 18 years of age, with opioids infusion ≥4 days. Exclusion: Not described.	Scale: WAT-1 Measurement every 12h and when required by clinical judgement. From the start of sedoanalgesia suspension to 3 days after the last dose of opioids.	Nurses' clinical judgement (Severity of the symptoms with numerical scale from 0-10).	Cut-off score: ≥3 Sensitivity: 87% Specificity: 88%	WAT-1 showed an excellent psychometric assessment in evaluating significant withdrawal symptoms.
Frank et al, 2012	Prospective multi-centre study of repeated measures	Assessing the validity, reliability and generalisation of the WAT-1	N = 308 children (mean of 1.5 years of age) Inclusion: Patients from 2 months up to 18 years, exposed to opioids ≥5 days. Exclusion: Not described.	WAT-1 scale measurement every 12 hours and in the event of IWS symptoms. From the start of withdrawal until 72h after the last dose of opioids.	No method used.	WAT-1 scores ≥3 had longer treatments with opioids, longer withdrawal periods, and higher accumulated doses.	WAT-1 showed an excellent psychometric assessment in evaluating significant withdrawal symptoms.

BZD = Benzodiazepines, H = Hours, IWS = Iatrogenic withdrawal syndrome, MDZ = Midazolam, NRS = Numerical Rating Scale, OBWS = Opioid and Benzodiazepine Withdrawal Score, SOS = Sophia Observation Withdrawal Symptoms, WAT-1 = Withdrawal Assessment Tool-Version 1.

deprivation.[22,23] The SOS has 15 items, each one corresponding to a withdrawal symptom, obtaining a positive score if the symptom has been observed at some point in 4 hours.[25] Table 5 summarizes the characteristics of these tools.

3.3. IWS treatment

Among the reviewed papers, 2 studies analyzed clonidine as a pharmacological treatment for IWS associated with continuous and prolonged infusion of benzodiazepines and opioids.[27,30] Two other studies examined methadone to reduce and prevent IWS caused by prolonged administration of opiates. Likewise, 1 study focused on phenobarbital and clonidine,[26] and another one on dexmedetomidine, as IWS treatments, when it was developed for the same previous causes.[24] Table 6 details the selected records that studied IWS treatments in critical paediatric patients for this review.

Three of them were descriptive studies and the other 3 were observational. These involved a total of 75 very heterogeneous patients. The demographic characteristics of these patients are reflected in Table 6. All subjects received multiple sedatives and analgesics during their hospital stay, being benzodiazepines and opiates the most usually employed ones. These were administered continuously for 37.92 ± 28.50 days in average, simultaneously with extra doses (boluses) of sedoanalgesia in case of loss of adaptation to the mechanical ventilation or given withdrawal indications in the process of withdrawal of these drugs. The sedoanalgesia treatment is described in Table 6.

Three different methods were used in the process of withdrawing the sedoanalgesia. On the one hand, in 2 of the reviewed studies, analgesia and sedation withdrawal were carried out progressively, according to the child's tolerance, until they were completely withdrawn.[27,30] On the other hand, 2 articles used sequential sedation prior to extubation of the patient, which consisted in converting doses of analgesics and opioids into equipotent doses of morphine, methadone or FNT, and MDZ, respectively. Then, they were withdrawn.[24,28] Finally, 2 studies applied the usual hospital units' protocol of sedoanalgesia withdrawal.[26,29] Table 7 details the sedoanalgesia withdrawal strategies.

3.3.1. Clonidine. Three studies analyzed the effects of clonidine on the IWS manifestations and as a prophylactic therapy for this phenomenon.

On the one hand, Ladrieri et al[30] compared withdrawal symptoms in subjects receiving transdermal clonidine and those who did not receive it. In his research, it was found that, 24 hours after the withdrawal of dexmedetomidine, patients without clonidine presented greater intensity of deprivation symptoms with a WAT-1: 3.2 score (range 0-8) vs 0.8 (range 0–6), ($P = .49$), as compared to patients who did have clonidine administered. The most pronounced symptoms in patients without clonidine were trembling, repetitive movements, startles, time to calm, increased muscle tone, and higher score in the Behavioural State Scale (BSS). No significant differences were observed in systolic (SBP) and diastolic (DBP) blood pressure figures, neither prior to the sedoanalgesia withdrawal ($P = .624$ and $P = .910$) and after this ($P = .851$ and $P = .678$), nor between both groups. However, the average heart rate (HR) in the clonidine group 24 hours after the withdrawal of sedoanalgesia was significantly lower than in the group without clonidine: 112 bpm (88.5–151.5) vs 138.4

Ávila-Alzate et al. Medicine (2020) 99:5

Medicine

Table 5

Main features of the IWS diagnostic tools.

	WAT-1	SOS	OBWS
Number of Items	11	15	21
Assessment method	Information on previous 12h 2 minutes before the ttm. 1 minute during the ttm. Post-ttm recovery.	At 4 am, 2 pm and 8 pm In the event of suspicious IWS 2h after IWS treatment.	Measurement every 4h, up to 2 days after sedoanalgesia suspension.
Musculoskeletal symptoms			
Muscle tone	✓	✓	
Startles	✓		✓
Trembling	✓	✓	✓
Repetitive movements	✓	✓	✓
Behaviour			
Previous state to the ttm.	✓		
Time to calm	✓		✓
GI symptoms			
Vomiting	✓	✓	✓
Diarrhoea	✓	✓	✓
Autonomic symptoms			
Fever	✓	✓	✓
Sweating	✓	✓	✓
Tachypnoea		✓	✓
Tachycardia		✓	
Pupil dilation			✓
CNS irritability			
Anxiety		✓	
Agitation		✓	✓
Other symptoms			
Yawning	✓		✓
Sneezing			✓
Nasal congestion			✓
Inconsolable crying		✓	✓
Grimacing		✓	
Insomnia		✓	✓
Hallucinations		✓	✓
Need for suction			✓
Cut-off score	≥ 3	≥ 4	≥ 8
Sensitivity (%)	87.2	83	50
Specificity (%)	88	93	87
Predictive validity (ROC)	0.94	0.95	0.82
LR			
Positive	Not reported	11	4
Negative	Not reported	0.19	0.57
Contrast assessment method	NWS	NRS	Nurses' clinical judgement
Correlation with contrast assessment method	SCC=0.80	SCC = 0.78 ($P <$ .0001)	SCC = 0.66 ($P =$ .007)
Correlation between reviewers (Cohen's Kappa coefficient)	0.80 (ICI = 0.98)	Not reported	Not reported

CNS = Central Nervous System, GI = Gastrointestinal, H = Hours, ICI = Interclass Correlation Index, IWS = Iatrogenic Withdrawal Syndrome, LR = Likehood ratio, NRS = Numerical Rating Scale, NWS = Neonatal Withdrawal Score, OBWS = Opioid and Benzodiazepine Withdrawal Score, ROC = Receiver Operating Characteristic, SCC = Spearman correlation coefficient, SOS = Sophia Observation Withdrawal Symptoms Scale, Ttm = Treatment, WAT-1 = Withdrawal Assessment Tool-Version.

bpm (range 117.8–168.3); $P =$ .03. Also, the HR mean change of pre-and post-discontinuation was significantly higher in the group without clonidine versus the clonidine group [29.9 bpm (range: 5.5–74.7) vs 3.6 bpm (range 39.6–47.5); $P = 0.042$]. Finally, rebound arterial hypertension was the only adverse effect related to clonidine.

On the other hand, Cho et al[27] employed clonidine to decrease the sympathetic activation of the patient. In this study, it was found that this was effective for lowering HR, RR, and blood pressure, and although they failed to eliminate the trembling, they did reduce its intensity. Finally, Weber et al[26] found that clonidine along with dexmedetomidine as prophylactic treatments for the IWS did not obtain results, presenting the subject fever, insomnia, extreme agitation, nervousness, and inconsolable crying 72 hours after the discontinuation of the sedoanalgesia.

3.3.2. Methadone. Two studies assessed methadone as IWS treatment in critically ill paediatric patients. In the study by Siddappa et al,[28] 66.6% (n = 20) of patients presented less than 3 withdrawal symptoms and, therefore, did not require additional doses of methadone. On the other hand, 33.3% (n = 10) of patients showed more than 3 signs of high intensity withdrawal, coming to need additional doses of this drug. Additionally, in this analysis, the optimal dose of methadone was determined to prevent the IWS and it was found that, with doses

Table 6

Description of the studies on pharmacological treatment of the IWS included in the review.

Author, year, design	Objectives	Sample (age)	Intervention	IWS assessment	Main outcomes	Conclusions
Siddappa et al, 2003 Cases and controls analysis with retrospective cohort	Assessing whether inappropriate methadone doses are withdrawal risk factors. Determining the appropriate methadone dose to prevent the IWS.	N = 30 children (0–16 years) Inclusion. Patients with FNT infusion for ≥7 days and who received methadone. Exclusion: post-extubation complications, other withdrawal therapies, severe brain injuries, inappropriate documentation and non-extubated 72 h after starting methadone treatment.	Methadone daily dose= FNT infusion dose × 3, every 8 h during 48 h. At 32 h, change from IVR to OR. Rescue dose: 10%–20% of IVR dose.	Nurses' clinical judgement	33,3% of patients experienced IWS, needing extra methadone doses. 80% of the proposed methadone dose was effective in decreasing withdrawal symptoms.	An inappropriate methadone dose is a risk factor for opioids withdrawal. The effective methadone dose is 2.4 times the daily fentanyl dose in mg.
Lugo et al, 2001 Post-protocol retrospective cohort study	Determining if enteral methadone can facilitate FNT suspension, and whether it prevents IWS in children.	N = 22 children (6.1 ± 5.4 years) with FNT infusion for ≥9 days. No inclusion and exclusion criteria described.	48h before FNT suspension, enteral methadone was administered in an initial dose of 0.1 mg/kg every 6h.	Medical body clinical criteria	FNT was suspended in a mean of 2.6 days. 4, 5% of patients developed the IWS, resolved by re-starting FNT and increasing methadone doses up to 0.3 mg/kg every 6h.	Enteral methadone can facilitate FNT suspension. It reduces the risk of withdrawal in critical children.
Lardieri et al, 2015 Retrospective analysis	Comparing IWS symptoms in patients with and without clonidine during prolonged dexmedetomidine infusions suspension.	N = 20 children (1.5 years [IQR: 0.67–33]) Inclusion. Patients of ≥42 weeks of GA and from 2 weeks to 18 years, with dexmedetomidine infusion for ≥5 days. Exclusion. Cyanotic cardiopathy, PHT, neuromuscular respiratory failure and MV dependence.	Transdermal clonidine (patches), with an initial dose of 100–50 μg/24h.	WAT-1 hemodynamic parameters.	Improvement of withdrawal symptoms intensity and less increased WAT-1 scores. No significant differences in blood pressure values; Significant differences were found in HR with clonidine.	Clonidine reduces withdrawal manifestations.
Cho et al, 2007 Case report	Presenting the IWS case. Stating the sedation strategies and prophylactic methods of the IWS.	N = 1 (6 years) Burn patient. Prolonged sedoanalgesia with MDZ and FNT (28 days)	Methadone 2mg OR 3 times a day. Clonidine with an initial dose of 0.05mg OR. 4 times a day.	Clinical criteria according to the patient's symptoms	Motor impairment, HR, BP and RR were reduced.	Professionals should acknowledge the new preventive strategies and treatments for the IWS associated with prolonged sedation.
Finkel et al, 2005 Case series	Describing the use of dexmedetomidine to facilitate sedoanalgesia suspension and assessing its impact on the heart.	N = 2 children (6 months y 7 years) Patients undergoing heart transplant and exposed to prolonged sedoanalgesia infusions.	Initial dexmedetomidine bolus 1μg/kg IVR in 10 min., followed by continuous infusion of 0.5–1 μg/kg/h for 8 days. Extra boluses of 1μg/kg in the event of withdrawal symptoms or every 6–8h.	UMSS and patient's symptoms criteria	Benzodiazepines and opioids suspension was successfully performed. Keeping hemodynamic stability.	Dexmedetomidine keeps hemodynamic parameters at satisfactory levels during opioids withdrawal in children with denervated hearts.
Weber et al, 2012 Case report	Describing the case of a child with sedoanalgesia and phenobarbital that presents severe withdrawal symptoms.	N = 1 child (11 months) Patient with MV, respiratory failure and prolonged sedoanalgesia with FNT, MDZ, morphine and phenobarbital.	Phenobarbital: Initial dose of 150 mg (14 mg/kg), followed by 5.6 mg/kg/day through OR. Clonidine: 8 μg/kg/day OR for 1 week, preceded by a 25% increase one more week.	PWI and patient's symptoms.	Choreiform movements decreased, as well as irritability and febrile peaks.	No conclusions reported.

Mean ± standard deviation (SD); Median [IQR] (Interquartile range).
APD=acute pulmonary disease, BDZ=benzodiazepines, BP=Blood pressure, FNT=fentanyl, GA=gestational age, H=hours, HR=Heart rate, IQR=Interquartile range, IVR=Intravenous route, IWS=iatrogenic withdrawal syndrome, MDZ=midazolam, mg=milligrams, MV=mechanical ventilation, NMB=neuromuscular blockers, OBWS=Opioid and Benzodiazepine Withdrawal Score, OR=oral route, PHT=pulmonary hypertension, PICU=paediatric intensive care units, PWI=paediatric withdrawal inventory, RR=Respiratory rate, SOS=Sophia Observation withdrawal symptoms, UMSS=University of Michigan Sedation Score, WAT-1=Withdrawal Assessment Tool-Version 1.

Table 7

Description of demographic characteristics, sedoanalgesia strategies and withdrawal regimes employed in studies on the pharmacological treatment of the IWS included in the review.

	Lardieri et al, 2015	Cho et al, 2007	Finkel et al, 2005	Weber et al, 2012	Siddappa et al, 2003	Lugo et al, 2001
Sample and weight	N = 20 Clonidine group: 12.3 kg (8–19)[†] No clonidine group: 9.8 kg (8.5–12.3)[†]	N = 1 25 kg	N = 2 5 and 14 kg	N = 1 10.4 kg	N = 30 IWS group: 24 kg (4.6–70)* Non-IWS group: 10kg (3.2–100)*	N = 22 22 ± 18.6 kg Clonidine group: 1.5 (0.67–33)[†] No clonidine group: 1 (0.85–1.3)[†]
Age (years)	Clonidine group: 1.5 (0.67–33)b No clonidine group: 1 (0.85–1.3)[†]	6	0.6 y 7	11	IWS group: 1.3 (0.1–15.3)* Non-IWS group: 7.7 (0.6–16.2)*	6.1 ± 5.4
Diagnosis at admittance	Respiratory failure, pneumonia, respiratory syncytial virus and asthma.	Severe burn and attention deficit disorder.	Pulmonary atresia, severe coronary stenosis, myocardial ischaemia, Barth syndrome, heart transplant.	congenital diaphragmatic hernia, pulmonary hypoplasia, pneumonia.	Not reported	Pneumonia, HI, septicaemia, trauma, heart surgery, respiratory failure, peritoneal abscess, BP and PH.
Therapeutic procedures	MV	MV, escharotomies, skin grafts and slough debridement	MV, heart transplant and ECMO	MV and ECMO	Not reported	MV
Hypnotics	DXD	MDZ	MDZ, LRZ	MDZ and PB	Not used	MDZ, DZM, PB, LRZ
Analgesics	Not reported	FNT	FNT, Methadone	FNT and morphine	FNT, SFT, RMF	FNT
Sedoanalgesia duration (days)	Clonidine group: 10 [7.7–17][†] No clonidine group: 5.5 [4.9–6][†]	48	84	42	IWS group: 12.5 (7–26)* Non-IWS group: 10 (7–41)*	17.8 ± 8.4
Hypnotics mean doses	1 μg/kg/h (0.53–1.81)*	Not reported	Not reported	Not reported	–	–
Analgesia mean doses	Not reported	Not reported	Not reported	Not reported	IWS group: 4.2 (1–10.5)a mg/kg Non-IWS group: 1.25 (0.5–5.9)a mg/kg	1302 (354–7535)* μg/kg
Maximum hypnotic doses	1.5 μg/kg/h [1-1.85][†]	0.8 mg/kg/h	Not reported	MDZ 0.25 mg/kg/h PB 3 mg/kg/h	–	–
Analgesic maximum doses	Not reported	20 μg/kg/h	Not reported	FNT 6 μg/kg/h Morphine 0.2 mg/kg/h	IWS group: 14 (7–55)*. Non-IWS group: 8.2 (4–117)*	5.9 ± 3.8 μg/kg/h
Suspension duration (days)	Clonidine group: 10 [IQR: 7.7-17] No clonidine group: 5.5 [IQR: 4.9–6]	Not reported	Not reported	14	IWS group: 0 (range: 0-1) Non-IWS group: 2 (range 0-8)	2.6 (range: 0–11.9)
Suspension regime	Decreasing DXD dose 0.2-0.5 μg/kg/h every 12hours, until reaching a dose of 0.2-0.5 μg/kg/h before suspension.	1% reduction of FNT dose and MDZ every hour, until reaching a 10% decrease per day, according to the patient's tolerance.	Abrupt discontinuation of MDZ, FNT, lorazepam and methadone.	Conversion of FNT in equivalent doses of 1:1 methadone, and MDZ to lorazepam 1:0.5. Propofol infusion of 250 μg/kg/h, together with 2 boluses of 0.7 μg/kg in 9 h.	Conversion of SFN and RMF to equivalent doses of FNT; likewise, with MDZ doses to lorazepam. Progressive reduction of FNT until suspension.	25–50% reduction of BZD in extubation. After 2–3 days, administration is decreased to every 8h for 2–3 days, followed by a 25% reduction of the original dose every 2-3 days until suspension.
Rescue in the event of IWS	Not needed	Clonazepam OR (posology and doses not stated)	Not needed	Restart of MDZ infusion with 0.05–0.1 mg/kg/h	Not needed	FNT infusion is restarted with 2 μg/kg/h
Treatment medications and prophylaxis	Clonidine (prophylaxis and treatment)	Methadone (prophylaxis) and clonidine (treatment)	Dexmedetomidine (prophylaxis and treatment)	Clonidine (prophylaxis) Phenobarbital (treatment)	Methadone (prophylaxis)	Methadone (prophylaxis)

* range.
[†] interquartile range.

BT = bacterial tracheitis, DXD = Ddexmedetomidine, DZM = diazepam, ECMO = extracorporeal oxygenation membrane, FNT = fentanyl, HI = head injury, IWS = iatrogenic withdrawal syndrome, LRZ = lorazepam, MDZ = midazolam, MV = mechanical ventilation, OR = oral route, PB = phenobarbital, PH = pulmonary haemorrhage, RMF = remifentanil, SFT = sufentanil.

≤80% of the used formula (methadone = 3× daily dose of fentanyl), withdrawal symptoms would occur in 23.3% (n = 7) of the subjects (OR: 21), and with a dose of >80% in 10% (n = 3). There were no secondary effects derived from methadone administration.

In the research by Lugo et al,[29] 95.5% (n = 21) of children did not present IWS during the decrease in fentanyl infusion. The only patient who developed IWS manifested diaphoresis, agitation, arterial hypertension (mean blood pressure: 90–100 mm Hg), diarrhoea, tachypnoea, disorientation, abdominal pain, and trembling. However, with an increase of 0.30 mg/kg in the dose of methadone every 6 hours, simultaneously with diazepam 0.1 mg/kg every 6 hours, the symptoms were resolved.

3.3.3. Phenobarbital.
Weber et al[26] developed the only study that assessed phenobarbital associated with clonidine as IWS treatment. The subject experienced cessation of choreiform movements, and decreased stress and fever after 2 days of the onset of phenobarbital. In addition, it reduced the need for additional doses of sedatives and analgesics, allowing to be withdrawn in less than a week. No adverse effects associated with this drug were developed.

3.3.4. Dexmedetomidine.
One study analyzed the use of dexmedetomidine to facilitate withdrawal of opioid analgesics.[24] In this research, this drug showed to be useful by decreasing sympathetic activation, reducing the heart rate from 135–176 bpm to 110–147 bpm, SBP mean from 90–150 mm Hg to 88–123 mm Hg, and slightly decreasing the DBP mean from 55–98 mm Hg to 50–70 mm Hg. Similarly, it eliminated disorganized movements and maintained the level of sedation, according to the ≤ 2 sedation score of the University of Michigan (UMSS). However, nausea was present on the fifth day of infusion of this medicine. Finally, rebound arterial hypertension was not reported when lowering the dose or after removing the dexmedetomidine.

4. Discussion

This review of the literature identifies 3 IWS assessment scales validated for the paediatric population and describes a clinical variability in relation to the diagnosis and treatment of the IWS. These results are of great relevance since the absence of an early and correct diagnosis of the IWS physically and psychologically affects patients' well-being and increases health expenditure.[6,33]

Harris et al[34] recommend the use of validated IWS assessment tools and whose reliability, validity and clinical utility have been tested and demonstrated in children. The WAT-1, SOS, and OBWS are validated scales. However, their items do not conform to the different paediatric ages. In the case of OBWS, the Moro reflex is included which, despite being a significant manifestation of withdrawal in newborns, disappears by 3 months of age.[35] WAT-1, on the contrary, does not include any specific symptoms at any stage of the child's development.[22,23] However, Frank et al[22] indicate that estimating each of these characteristics would seriously compromise the utility of the tool. Consequently, future research to define a new IWS assessment tool for collecting the specific manifestations at each age or for carrying out adaptations of the existing scales for each stage of development are necessary.

In relation to the statistical characteristics, it was found that the WAT-1 and the SOS possess high sensitivities and specificities, and have similar psychometric characteristics.[22,23,25] The

OBWS, on the contrary, presents an excellent specificity but a reduced sensitivity, which translates into a low capacity for the scale to detect the IWS in really sick children and high competence in ruling out the disease in healthy subjects.[32] On the other hand, the SOS and WAT-1 obtained a greater diagnose accuracy against the OBWS, reflected with higher areas below the ROC curve.[22,23,25,32] Finally, the SOS is a scale with a high possibility of making strong changes in the pre and post-test probability.[25] However, the OBWS showed good predictive validity and, according to its likelihood ratio, it is an acceptable diagnostic test which slightly increases the probability of a positive diagnosis of the IWS.[32]

In addition, none of the 3 instruments, despite contemplating different signs and symptoms of withdrawal, can discern between the IWS caused by opioids and the IWS caused by BZD.[11,23,25] However, Franck et al[23] suggest that WAT-1 is more effective in detecting symptoms of opioid withdrawal than in detecting symptoms of BZD withdrawal. This may be because, unlike the SOS and OBWS, this scale does not contemplate the specific withdrawal manifestations to these sedatives: hallucinations, grimaces, and considerable disorganized movements.[11,25,32,36] It could even be said that the SOS is more sensitive than the OBWS in detecting BZD withdrawal manifestations because, in addition to assessing the hallucinations and alterations of the movement, it also comprises facial expressions.[25,32] Finally, the WAT-1 faces this drawback by incorporating in its items the SBS, which requires a painful stimulus for its assessment.[22,23]

In this review, clonidine was revealed to be effective in subsiding withdrawal symptoms from sedoanalgesia. On the one hand, Ladrieri et al[30] employed transdermal clonidine and, on the other hand, Cho et al[27] and Weber et al[26] used it in an enteral way, achieving similar effects and even facilitating the withdrawal of opioid analgesics, although it was not possible to eliminate the trembling.

Additionally, in the Weber et al study,[26] clonidine did not have the expected prophylactic effect, and the IWS was triggered. Therefore, it might be suggested that transdermal clonidine is slightly more effective than enteral. This fact can be attributed, first, to the lower tissue infusion of the organs existing in critical patients which in turn causes atrophy and reduction of gastrointestinal motility. This translates into the decrease of the gastrointestinal absorption of the medicine.[17] Secondly, it has been observed that clonidine has a greater prophylactic utility for the IWS in the first 24 hours after the withdrawal of sedation, especially in children with respiratory failure.[30] Third, in several studies, it has been shown that transdermal clonidine is safer since it provides constant doses and, in turn, reduces peak doses and adverse reactions.[27,30,31]

The results of the reviewed articles are consistent with the review conducted by Duffet et al[37] on the effect of clonidine on sedation and withdrawal symptoms. In this review, it was described that with the use of clonidine, a reduction in withdrawal manifestations was obtained, along with an increase in the level of sedation and the need for sedatives. However, these results may be limited by the small sample size, the lack of precision to estimate the effect of clonidine, and the heterogeneity of the included studies.

According to the reviewed studies, methadone managed to reduce and prevent the IWS, with scarce side effects. Siddappa et al[28] converted the dose of intravenous fentanyl into equipotent doses of methadone that were subsequently enterally administered. This practice has been recommended and used by

several researchers.[6,38,39] However, most of these formulas were made from the pharmacokinetic characteristics of healthy subjects.[40] In addition, regarding changes in the route of administration, it is necessary to consider the capacity of fentanyl (100 times greater than methadone) and the average life and the bio-viability of methadone (75%–100% and 75%–80%).[6] On the contrary, Lugo et al,[29] despite the previous recommendations, used a minimum initial dose of methadone, increased if necessary. It is argued that, even considering the capacity and average life of both drugs, the resulting equivalent dose is higher than the dose needed to prevent the IWS, thus lengthening dependence and opiates withdrawal time.[29]

This review identified a lack of agreement in relation to the most suitable initial dose to prevent the IWS. On the one hand, Siddappa et al[28] recommended 2.4 times the dose of fentanyl every 6 hours, in contrast to Lugo et al,[29] who proposed a dose of 0.1 mg/kg every 6 hours. However, Johnson et al,[40] in their review, advised more frequent intervals of administration, reaching ranges of 3.8 to 62 hours. According to the above-mentioned, using smaller intervals between doses seems to be more effective to achieve therapeutic concentrations in a more precocious way.

Dexmedetomidine was used in a descriptive study included in this review for the purpose of facilitating withdrawal of opiates in 2 hospitalized children in a PICU with denervated hearts by cardiac transplantation.[24] The initially used dexmedetomidine doses were recommended for adults and, in the event of withdrawal symptoms, additional boluses of dexmedetomidine were administered.[24] The use of non-paediatric doses responds to the lack of studies on the use of dexmedetomidine in children with transplanted hearts. So far, it had only been proven to be used in animals with similar characteristics. However, the results partly coincide with another descriptive study in which the dexmedetomidine effectively controlled the manifestations of the IWS without producing hemodynamic disturbances.[31]

Phenobarbital, like other IWS treatments, managed to eliminate withdrawal signs and symptoms, being this a case of resistant IWS to other treatments such as dexmedetomidine, clonidine and methadone. In the case of dexmedetomidine, a loading dose was not administered, being this, a priori, the reason for its ineffectiveness.[24] There are studies that prove that the efficacy of dexmedetomidine depends both on the loading dose and on the procedure of its withdrawal.[31]

Finally, in this review, the relevance of the appropriate dosage administration in all the analyzed IWS treatments was proven. This is because, regardless of the drug used, an excessive or insufficient dose increases the risk of IWS. Likewise, the withdrawal regime must be closely controlled and set by objectives, with the purpose of not developing the IWS through the same drug that was administered to prevent it.

4.1. Limitations

This review has several limitations: due to the limited number of studies, subjects, and the diversity of variables (sedoanalgesia regimen, IWS assessment, concomitant use of other drugs, polypathological patients, and interventions), it is difficult to quantify the effect of the analyzed treatments. Another obvious limitation is the moderate quality of the data and the scarce evidence of the analyzed articles, since they include prospective and descriptive observational studies without including any clinical trial, which may be due to the shortage of literature on

this research topic. However, all references were submitted to an assessment of their methodological quality in order to identify their limitations and biases.

5. Conclusions

In this review, 3 diagnostic and assessment scales of the IWS with sedatives and/or narcotic analgesics in clinically ill paediatric patients have been identified: WAT-1, SOS, and OBWS. All these tools are validated and have good predictive and diagnostic qualities. WAT-1 and OBWS have similar psychometric properties and are more effective than the SOS in the detection of the IWS. On the other hand, nurses are essential in the diagnosis of the IWS and they perceived the OBWS as a useful tool in the detection and assessment of this phenomenon. The use of validated IWS valuation scales in paediatrics' clinical practice should be encouraged, and the nursing staff should be trained in their usage.

Regarding IWS treatments related to prolonged administration of hypnotics and opiates in hospitalized children in critical care units, clonidine proved to be effective in preventing, palliating, and decreasing the intensity of withdrawal symptoms from both opioids and hypnotics, especially by subsiding sympathetic activation. However, it may cause rebound arterial hypertension as an adverse effect, although this is rare.

On the other hand, enteral and parenteral methadone reduce the risk of IWS produced by opioids, facilitate the discontinuation, and alleviate withdrawal manifestations after the suspension. Dexmedetomidine was not only efficient in reducing the opioid withdrawal symptoms, even in patients with cardiac transplantation. In addition, it facilitated the withdrawal of these analgesics while maintaining a hemodynamic stability. Finally, phenobarbital is efficient in alleviating and reducing the intensity of opioids and BZD withdrawal symptoms, that are resistant to other therapies.

To conclude, the literature on paediatric IWS assessment tools and the pharmacological treatment of this syndrome is scarce. Consequently, future research on these issues is necessary to develop a more complete comparison of the effectiveness of reviewed scales and treatments. In the same way, a more effective management and assessment of the IWS could be achieved, as well as the determination of its prevalence in the paediatric population in a more reliable way.

Author contributions

Conceptualization: Jennihe Alejandra Ávila-Alzate, Santiago Martínez-Isasi.
Data curation: Jennihe Alejandra Ávila-Alzate, Macarena Romero-Martín, Daniel Fernández-García.
Formal analysis: Jennihe Alejandra Ávila-Alzate, Macarena Romero-Martín, Daniel Fernández-García.
Investigation: Juan Gómez-Salgado, Santiago Martínez-Isasi, Daniel Fernández-García.
Methodology: Jennihe Alejandra Ávila-Alzate, Juan Gómez-Salgado, Macarena Romero-Martín, Santiago Martínez-Isasi, Daniel Fernández-García.
Project administration: Jennihe Alejandra Ávila-Alzate.
Resources: Juan Gómez-Salgado, Macarena Romero-Martín, Daniel Fernández-García.
Supervision: Jennihe Alejandra Ávila-Alzate, Juan Gómez-Salgado, Santiago Martínez-Isasi.

Validation: Juan Gómez-Salgado, Santiago Martínez-Isasi.
Visualization: Jennihe Alejandra Ávila-Alzate, Macarena Romero-Martín, Santiago Martínez-Isasi.
Writing – original draft: Jennihe Alejandra Ávila-Alzate, Macarena Romero-Martín, Daniel Fernández-García.
Writing – review & editing: Juan Gómez-Salgado, Santiago Martínez-Isasi.

References

[1] Burastero M, Telechea H, González S, et al. Incidencia del síndrome de abstinencia en niños críticamente enfermos. Arch Pediatr Urug 2017;88:6–11.
[2] Mencía S, Botrán M, López-Herce J, et al. Grupo de Estudio de Sedoanalgesia de la SECIPManejo de la sedoanalgesia y de los relajantes musculares en las unidades de cuidados intensivos pediátricos españolas. An Pediatr 2011;74:396–404.
[3] Dreyfus L, Javouhey E, Denis A, et al. Implementation and evaluation of a paediatric nurse-driven sedation protocol in a paediatric intensive care unit. Ann Intensive Care 2017;7:36.
[4] Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. Crit Care Med 2014;42:1592–600.
[5] Curley MAQ, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA 2015;313:379–89.
[6] Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 2000;28:2122–32.
[7] Fernández-Carrión F, Gaboli M, González-Celador R, et al. Síndrome de abstinencia en Cuidados Intensivos Pediátricos. Incidencia y factores de riesgo. Med Intensiva 2013;37:67–74.
[8] Hammer GB. Sedation and analgesia in the pediatric intensive care unit following laryngotracheal reconstruction. Paediatr Anaesth 2009;19:166–79.
[9] Hronová K, Pokorná P, Posch L, et al. Sufentanil and midazolam dosing and pharmacogenetic factors in pediatric analgosedation and withdrawal syndrome. Physiol Res 2016;65:S463–72.
[10] Grant MJ, Balas MC, Curley MAQ. Defining sedation-related adverse events in the pediatric intensive care unit. Heart Lung 2013;42:171–6.
[11] Ista E, van Dijk M, Gamel C, et al. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. "Assessment remains troublesome". Intensive Care Med 2007;33:1396–406.
[12] Best KM, Boullata JI, Curley MAQ. Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: A systematic review and conceptual model. Pediatr Crit Care Med 2015;16:175–83.
[13] Playfor S, Jenkins I, Boyles C, et al. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med 2006;32:1125–36.
[14] Anand KJS, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically Ill children. Pediatrics 2010;125:e1208–25.
[15] Best KM, Wypij D, Asaro LA, et al. Patient, process and system predictors of iatrogenic withdrawal syndrome in critically ill children*. Crit Care Med 2017;45:e7–15.
[16] Fisher D, Grap MJ, Younger JB, et al. Opioid withdrawal signs and symptoms in children: Frequency and determinants. Heart Lung 2013;42:407–13.
[17] Honey BL, Benefield RJ, Miller JL, et al. α2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother 2009;43:1506–11.
[18] Urrútia G, Bonfill X. Declaración PRISMA: una propuesta para mejorar la publicación de revisiones sistemáticas y metaanálisis. Med Clin 2010;135:507–11.
[19] Cabello JB. Plantilla para ayudarte a entender estudios de cohortes. In CASPe. Guías CASPe de Lectura Crítica de la Literatura Médica. Alicante: CASPe; cuaderno II; 2005;23–7.
[20] Cabello JB. Plantilla para ayudarte a entender un Estudio de Casos y Controles. In CASPe. Guías CASPe de Lectura Crítica de la Literatura Médica. Alicante: CASPe; cuaderno II; 2005;13–9.
[21] Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med 2013;2:38–43.
[22] Franck LS, Scoppettuolo LA, Wypij D, et al. Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. Pain 2012;153:142–8.
[23] Franck LS, Harris SK, Soetenga DJ, et al. The Withdrawal Assessment Tool - Version 1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. Pediatr Crit Care Med 2008;9:573–80.
[24] Finkel JC, Johnson YJ, Quezado ZMN. The use of dexmedetomidine to facilitate acute discontinuation of opioids after cardiac transplantation in children. Crit Care Med 2005;33:2110–2.
[25] Ista E, de Hoog M, Tibboel D, et al. Psychometric evaluation of the sophia observation withdrawal symptoms scale in critically ill children. Pediatr Crit Care Med 2013;14:761–9.
[26] Weber GM, Smerling AJ, Saroyan JM. Pentobarbital withdrawal and treatment in an infant in the pediatric cardiac intensive care unit. J Clin Anesth 2013;25:62–5.
[27] Cho HH, O'Connell JP, Cooney MF, et al. Minimizing Tolerance and Withdrawal to Prolonged Pediatric Sedation: Case Report and Review of the Literature. J Intensive Care Med 2007;22:173–9.
[28] Siddappa R, Fletcher JE, Heard AMB, et al. Methadone dosage for prevention of opioid withdrawal in children. Paediatr Anaesth 2003;13:805–10.
[29] Lugo RA, MacLaren R, Cash J, et al. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. Pharmacotherapy 2001;21:1566–73.
[30] Lardieri AB, Fusco NM, Simone S, et al. Effects of clonidine on withdrawal from long-term dexmedetomidine in the pediatric patient. J Pediatr Pharmacol Ther 2015;20:45–53.
[31] Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. J Opioid Manag 2006;2:201–5.
[32] Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. Intensive Crit Care Nurs 2004;20:344–51.
[33] Keogh SJ, Long DA, Horn DV. Practice guidelines for sedation and analgesia management of critically ill children: a pilot study evaluating guideline impact and feasibility in the PICU. BMJ Open 2015;5:e006428.
[34] Harris J, Ramelet AS, Van Dijk M, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med 2016;42:972–86.
[35] Domínguez KD, Lomako DM, Katz RW, et al. Opioid withdrawal in critically ill neonates. Ann Pharmacother 2003;37:473–7.
[36] Ista E, Van Dijk M, Gamel C, et al. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: afirst evaluation. Crit Care Med 2008;36:2427–32.
[37] Duffett M, Koop A, Menon K, et al. Clonidine for the sedation of critically ill children: a systematic review. J Pediatr Intensive Care 2012;1:5–15.
[38] Robertson RC, Darsey E, Fortenberry JD, et al. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. Pediatr Crit Care Med 2000;1:119–23.
[39] Bowens CD, Thompson JA, Thompson MT, et al. A trial of methadone tapering schedules in pediatric intensive care unit patients exposed to prolonged sedative infusions. Pediatr Crit Care Med 2011;12:504–11.
[40] Johnson PN, Boyles KA, Miller JL. Selection of the initial methadone regimen for the management of iatrogenic opioid abstinence syndrome in critically ill children. Pharmacother 2012;32:148–57.