Iatrogenic withdrawal syndrome frequently occurs in paediatric intensive care without algorithm for tapering of analgosedation

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Background: Analgesics and sedatives are key elements to reduce physiological and psychological stress associated with treatment in paediatric intensive care. Prolonged drug use may induce tolerance and development of iatrogenic withdrawal syndrome (IWS) during the tapering phase. Our primary aim was to describe the prevalence of IWS among critically ill ventilated patients in two Norwegian paediatric intensive care units (PICUs), and secondary to investigate what motivated bedside nurses to administer additional drug doses.

Methods: Mechanically ventilated patients (n = 40) from newborn to eighteen years of age, with continuous infusions of opioids and benzodiazepines for 5 days or more, were included consecutively from May 2016 to June 2018. By using Withdrawal Assessment Tool-1 (WAT-1) twice daily we recorded the prevalence of IWS. Additionally, we recorded signs and symptoms that led bedside nurses to administer extra bolus medication.

Results: Peak WAT-1 score indicated an IWS prevalence of 95% in this selected group. The first days of the tapering phase were most critical for IWS. The most frequent symptoms triggering administration of additional bolus doses were agitation/restlessness, and thiopental and propofol were the bolus drugs used most frequently.

Conclusions: IWS affected 95% of the children having received infusions of opioids and benzodiazepines for 5 days or more in PICUs without a tapering protocol for these drugs. This calls for implementation and testing of such weaning protocols.

Editorial Comment
Sedation over longer periods in paediatric intensive care is often associated with challenges concerning both drug tolerance and clinical signs of drug withdrawal when changing drugs or reducing drug doses. This study assesses an instrument for standardized assessment of clinical signs of withdrawal syndrome during drug weaning in this setting.

INTRODUCTION

Children receiving intensive care treatment risk complications related to the severity of their illness and the complexity of the treatment. Analgesation with opioids and benzodiazepines is provided to ensure an acceptable level of comfort for the patient, to alleviate pain and anxiety, and to avoid accidental removal of lifesaving tubes and lines. Use of these drugs for more than a few days...
may induce tolerance, physical dependence and development of iatrogenic withdrawal syndrome (IWS) in the tapering phase.\textsuperscript{3} IWS is defined as an adverse drug response with a pattern of signs and symptoms including central nervous system hyperirritability, gastrointestinal dysfunction and an autonomic dysfunction when an analgesic or sedative drug is abruptly stopped, sharply decreased or antagonized in a patient who is physically tolerant.\textsuperscript{2,5} Central nervous system affections include irritability, increased wakefulness, tremulousness, hyperactive deep tendon reflexes, clonus, frequent yawning, sneezing, delirium and hypertonicity.\textsuperscript{3} Activation of the autonomic nervous system may result in tachycardia, hypertension, tachypnea, sweating and fever.\textsuperscript{3} Gastrointestinal dysfunction may lead to feeding intolerance with vomiting and diarrhoea.\textsuperscript{2} Many of the IWS signs and symptoms will overlap with symptoms related to the child’s disease and also with symptoms of delirium.\textsuperscript{6} Therefore, a careful assessment using a validated tool is essential to detect IWS.\textsuperscript{7}

Two instruments for assessing IWS in children, the Withdrawal Assessment Tool-1 (WAT-1)\textsuperscript{8,9} and Sophia Observation Withdrawal Symptoms-scale (SOS)\textsuperscript{10,11} are recommended in guidelines.\textsuperscript{12} The frequency of mixed IWS in prospective studies range from 37% to 77% using WAT-1 and from 18% to 100% using SOS.\textsuperscript{13}

Most researchers using WAT-1 use Peak WAT-1 in their analysis when assessing IWS.\textsuperscript{8,14} However, Peak WAT-1 might not reflect the degree to which patients are bothered during the tapering phase because only one WAT-1 score from each patient is used in the analyses. To supplement Peak WAT-1, we decided to present also the sum of elevated WAT-1 scores (Sum WAT-1 ≥3) recorded during the study period to better describe the IWS burden over time.

The primary aim was to describe the prevalence and severity of IWS among severely ill patients in two Norwegian PICUs, and secondary, to investigate the causes that led bedside nurses to administer additional bolus doses of sedatives or analgesics.

## 2 | MATERIALS AND METHODS

### 2.1 Study design and setting

This prospective, observational study was designed to yield baseline data on IWS from two medical–surgical PICUs with six and three staffed beds at Oslo University Hospital, Norway. The PICUs did not have algorithms in place for tapering opioids and benzodiazepines. The health care providers did not use any monitoring tool to assess withdrawal signs and symptoms, just their professional judgement. The physicians decided how and when to taper when the patients were recovering. The plan is to re-do the study once tapering algorithms have been implemented within the units.

### 2.2 Ethics

The Regional Committees for Medical and Health Research Ethics approved the study (2016/135) and the parents provided written informed consent. ClinicalTrials.gov Identifier: NCT02952846.

### 2.3 Inclusion and exclusion criteria

All consecutive patients <18 years requiring mechanical ventilation and continuous infusion of opioids and/or sedatives for ≥5 days were eligible for enrolment. Enrolment was not precluded by the use of other sedative agents: eg, clonidine, dexmedetomidine, alimemazine, propofol, thiopental, levomepromazine, chloral hydrate, phenobarbital or ketamine.

Exclusion criteria were severe nervous system impairment that could affect assessment of the sedation level. Patients were included only once, and when the patient’s physician decided to initiate tapering. Data collection was closed if the patient was transferred to another hospital.

### 2.4 Study population

We aimed at recruiting 40 consecutive patients when tapering was initiated, and to follow these patients in PICU and general ward until 3 days after all analgosedation was stopped, however, with a limitation of maximum 21 days.

### 2.5 Data collection

Data collection included patient demographics and clinical characteristics. We selected WAT-1 as our monitoring tool because a Norwegian version was available and seemed convenient to use at the bedside.\textsuperscript{15} The tool was translated to Norwegian by following an established protocol for forward and backwards translation in collaboration with the originator Linda Franck. The WAT-1 score is an 11-item (12-point) instrument that screens for signs and symptoms of opioid- and benzodiazepine-related IWS in PICUs.\textsuperscript{8,7} The total score is a sum of all 11 items where a score ≥3 indicates IWS.\textsuperscript{8}

Sum WAT-1 ≥3 is calculated by adding all scores ≥3 during the tapering period. The number of scores included per day was fixed and pre-defined. We included two scores per day, one recorded between 7 and 10 o’clock in the morning, and the second between 5 and 7 o’clock in the afternoon.

The use of WAT-1 was not a part of the daily standard of care in the two units. Accordingly, members of the study group (MD, FEF, RIH, GAR, GKB) were trained in the use of the tool and conducted WAT-1 scores twice daily from the first day of tapering and continued until 72 hours after the last dose of analgesic or sedative was administered, but limited to 21 days. Unfortunately we were not able to measure inter-rater-reliability, but we trained in the use of WAT-1 together, and individual. We also discussed how to use the tool with the professionals who translated the WAT-1 tool into Norwegian, and with the originator of the tool, Linda Franck.

### 2.6 Detection of symptoms and signs that led to bolus medication

A questionnaire for day, evening and night shift staff was developed to record signs and symptoms that motivated bedside nurses to...
administer additional bolus doses of analgesics and/or sedatives. The questionnaire included: sleep disturbance, tremors, seizures, fever, muscle-contracting, hallucinations, crying, agitation/restlessness, sneezing, tachycardia, tachypnoea, hypertension, agitation, loose stools, nausea and vomiting. The nurses picked from the patients pro re nata (PRN) orders, and often they had a choice between opioids, benzodiazepines and other medication, such as propofol and thiopental. The nurses documented what motivated additional medication and recorded the type and dose of medications administered.

2.7 | Statistical analyses

Patient characteristics are reported as medians and interquartile ranges (IQRs) and ranges. Frequencies and percentages are given for categorical variables. Sum WAT-1 ≥3 was used in our analysis together with the Peak WAT-1 score. We used the closest number in cases with missing values when we summed the WAT-1 scores ≥3. For example, if the morning value was missing and the child scored 4 in the evening, we set 4 in the morning. For Peak WAT-1 missing values are not an issue, only the highest value recorded is used.

Distributions of Sum WAT-1 ≥3, Peak WAT-1 and patient characteristics were explored and checked for normal distribution by using histograms and quantile-quantile plots. The correlation between characteristics were explored and checked for normal distribution by using Spearman's correlation analysis. We used the bootstrap method of percentile to estimate the 95% confidence interval which was based on 1000 replications/bootstraps. Before conducting the analysis of association, Sum WAT-1 ≥3 and Peak WAT-1 scores were categorized into two groups using the medians as the cut-offs because of non-normality and non-monotone covariation between drugs, Peak WAT-1 and Sum WAT-1 ≥3. Patients with Sum WAT-1 ≥3 and Peak WAT-1 above the median value was allocated to the moderate/severe level group. The remaining patients were allocated to the absent/mild level group. The associations between patient characteristics, dose of drug infused, and the categorized groups were inspected by using Mann-Whitney-Wilcoxon tests. The tests were two-sided, and the significance level was set at .05. The analyses were performed with IBM SPSS Statistics software (v. 25; IBM SPSS).

3 | RESULTS

3.1 | Characteristics of the children

The sample comprised 40 children, 20 girls and 20 boys (Table 1). A total of 42 children were assessed for inclusion, but for two, their parents declined participation. The median age was 6 months (range, 5 days–9 years). Thirty-three patients (80%) were younger than 2 years and nine patients were newborn. The patients had a wide range of diagnoses: eg, infants with various congenital malformations such as gastroschisis, oesophageal atresia, omphalocele, diaphragmatic hernia, volvulus and neonatal sepsis. Twelve patients (30%) had an infectious disease such as bronchiolitis or sepsis. Nineteen patients had a wide range of rare diseases such as biliary atresia, DiGeorge syndrome, Apert syndrome and severe combined immune deficiency. We categorized the patients into groups based on the main reason for PICU admission (Table 1).

3.2 | Prevalence of IWS during the tapering phase

We conducted 1175 twice daily WAT-1 scores on 40 children, and 95% of the children had a Peak WAT-1 score of ≥3 during the study period (Figure 1). The median Peak WAT-1 score was 5 (IQR 3). The median Sum WAT-1 ≥3 score was 15.5 (IQR 31). This number indicates that the majority of the patients suffered from IWS on at least two scoring points, in practice for more than 24 hours. The Spearman's correlation coefficient between Peak WAT-1 and Sum WAT-1 ≥3 was 0.8 (CI 0.65, 0.89). As outlined in Table 2, the correlation between explanatory variables and outcome variables was different regarding some medication variables when we compared Peak WAT-1 and Sum WAT-1 ≥3 groups.

In the beginning of the tapering phase the patients were most at risk for developing IWS (Figure 2). Seven patients were readmitted to PICU during the tapering phase, one readmission was due to IWS. This patient scored 8 on WAT-1 on her return. Other adverse events were considered not to be related to IWS because the patients needed additional analgosedation arising from complications associated with their illness. Seven patients were reintubated due to respiratory failure, six had additional surgery, five patients needed another general anaesthesia, one patient needed a change of wound.
dressing, and one patient had a pneumothorax. Data collection was continued regardless of re-admission and reasons for this. The patients were followed for a maximum of 21 days and 22 patients were successfully tapered within that timeframe. Fifteen patients needed more than 21 days and three patients were discharged from the hospital before the 21 days of data collection was completed.

3.3 | Symptoms and signs that led to administration of additional bolus doses

The most frequent symptoms motivating additional doses of bolus medications were most frequently agitation/restlessness (34 patients) and sleep disturbance (32 patients), and the most frequent sign was tachycardia (Figure 3). The bedside nurses’ most frequent choice of bolus medication was propofol and thiopental (Table 3).

4 | DISCUSSION

4.1 | Prevalence of iatrogenic withdrawal syndrome

The main finding in the present study is an IWS prevalence of 95% based on Peak WAT-1 scores ≥3. Another important finding was that the most frequent drug used as rescue medication to treat IWS was thiopental and propofol.

IWS in studies with a similar research design has been reported to be between 47% and 77%.8,14,16 The use of Peak WAT-1 ≥3 in the present study is in accordance with the recommendation by Franck et al8 who found an IWS rate of 77% using inclusion criteria similar to those used here.8 The high prevalence of IWS in our study was unexpected. This could be because the group we have studied here, the patients receiving infusions of opioids and benzodiazepines for 5 days or more before tapering, accounts for only a very small portion of the total PICU population. It is easily done in day to day practice to overlook the major problem IWS represents for a small number of patients. This is not revealed before one actually checks using a monitoring tool. When it comes to the WAT-1 scoring tool, we think that it’s possible that the cut-off score of ≥3 is too low. Patients may be scored higher than 2 in a PICU setting even without the presence of IWS. The children may have several overlapping symptoms with clinical signs of pain, distress and anxiety. Furthermore, loose stools and vomiting may have causes other than IWS. Fever is also a sign with different other possible aetiologies, such as infection, overheating in the incubator or tucking-in the child too tightly. These concerns have also been discussed by other researchers17 and consequently, Amirnovin et al18 and Nelson Sanchez-Pinto et al19 increased the WAT-1 cut-off value to ≥4 in their research. That said, raising the cut-off to ≥4 in our material would have little influence on the observed prevalence (Figure 1). Our IWS prevalence would have been 82.5%.

4.2 | Peak WAT-1 and Sum WAT-1 ≥3

It is our perception that relying only on Peak WAT-1 when assessing the burden of IWS in a population is sub-optimal. Peak WAT-1 does not adequately represent a long lasting burden of IWS in an individual child, because only one single peak value is utilized. We assume that by using all the elevated WAT-1 scores ≥3, we get a valuable supplement to the use of Peak WAT-1 in the analysis. Using repeated measures, the Sum WAT-1 ≥3 represents “the area under the curve” for IWS in each patient, capturing both severity and duration. As shown in Table 2, the explanatory variables and drug variables differ between Peak WAT-1 and Sum WAT-1 ≥3 groups. The variables that were significantly associated with a more severe IWS by using Sum WAT-1 ≥3 were total hospital stay, PICU post-inclusion stay and duration of weaning (days) (Table 2). In this small sample, we therefore suggest that Sum WAT-1 ≥3 better discriminates between absent/mild IWS and moderate/severe IWS compared to Peak WAT-1. Total hospital stay and number of tapering days are recognized explanatory risk factors and our findings thus concur with results in earlier research articles.7,8,20
However, difference in the number of days on mechanical ventilation or non-invasive positive pressure ventilation did not reach significance (Table 2).

### 4.3 Risk of benzodiazepine, opioid and clonidine use

Several studies have shown that high cumulative doses of benzodiazepines and opioids are risk factors for developing IWS. Best et al.\(^6\) found that children exposed to a pre-weaning cumulative benzodiazepine dose of 16.0 mg/kg (IQR 8.5-31.5) had significantly more withdrawal symptoms, which is similar to our findings when based on the moderate/severe Peak WAT-1 level group (N = 15) (Table 2). Amigoni et al.\(^7\) found that the only variable that predicted IWS was the highest administered dose of benzodiazepine. The WAT-1 positive group in their sample had a cumulative benzodiazepine load of 24 mg/kg (IQR 10-36.1), also in agreement with our findings (Table 2).

On the other hand, Da Silva et al.\(^20\) found a low IWS rate (22.6%), even though the cumulative doses of midazolam in the IWS group were median 70.4 mg/kg (IQR 41.7-106.2). The reason for such high...
doses of midazolam might be that the children exclusively received midazolam and fentanyl for sedation in their study. Normally, PICU patients receive different types of analgosedation. In the present study, the Peak WAT-1 group scoring >5 (moderate to severe IWS) was exposed to 23.8 mg/kg (IQR 12.8-39.2) midazolam and if we use Sum WAT ≥3 (value >16), the dose was 15.7 mg/kg (IQR 10.7-30.7) (Table 2). High doses of midazolam were significantly associated with a more severe IWS when we used the Peak WAT-1 (P = .010), but was
not significant using Sum WAT-1 ≥3 (P = .668). This could suggest that midazolam is not the most problematic drug in this small selection of patients. This finding would be in agreement with that of Da Silva et al, who described low IWS prevalence even with exposure to very high doses of midazolam. 

Fentanyl was used as the first line opioid in the present study. As outlined in Table 2, the dose of fentanyl before weaning was associated with severe IWS when using the variable Sum WAT-1 ≥3 (P = .044). Earlier research has shown that fentanyl increases the risk of developing IWS. The association of IWS with the pre-tapering dose of fentanyl, but not midazolam in our study, points to fentanyl as more likely to promote a more long lasting IWS (Table 2). This observation is consistent with findings reported by Amigoni et al. They further reported that patients receiving morphine as their primary analgesic were 83% less likely to develop IWS than those receiving fentanyl or remifentanil in their multicenter study. Our small study can neither support nor refute these findings as very little morphine was given before tapering in our patients (Table 2). It would be very relevant to follow-up this observation in future studies.

In the present study, some children received clonidine during the entire course, but only to a limited extent before tapering of analgosedation (Table 2). A high total dose of clonidine was significantly associated with a more severe IWS (P < .001) (Table 2). Thus, we believe that clonidine was used in this sample when tapering of opioids and benzodiazepines was observed to be problematic. In fact, clonidine is widely used to prevent IWS in the weaning phase, but evidence of its effectiveness is limited. In a recent systematic review, dexmedetomidine and clonidine were deemed as options for the treatment and prevention of IWS, but the finding did not reach statistical significance. The use of clonidine may lead to a reduction in total doses of midazolam and fentanyl given in PICU. Another drug used in preventing and treating opioid withdrawal is methadone, and in a paper from 2020, the authors determine that this medication can be safely used in PICU, and is recommended in guidelines. However, in our PICUs, we have no tradition for the use of methadone.

### 4.4 Symptoms and signs that led to administration of extra bolus medicine

The most frequent symptoms that led to administration of extra bolus medicine were agitation/restlessness, sleep disturbance and crying, and the most frequent sign was tachycardia (Figure 3). Normally the bolus medication, called rescue medicine in IWS treatment, is an opioid or a benzodiazepine, but in our sample the nurses frequently administered propofol and thiopental. This is a practice also reported by others. A web-based survey from United Kingdom showed that propofol (89%) was the most common choice of sedative, followed by midazolam and morphine (49%). Propofol and thiopental are short- and rapid-acting medications, a simple choice in a busy everyday PICU, especially if the patients are awake with symptoms as agitation, crying and sleep disturbance, and they pose a risk of pulling out invasive equipment. This extensive use of propofol and thiopental may, however, have contributed to the high prevalence of IWS found in our study (Table 3).

### 4.5 Clinical implications

IWS may lead to a complex array of signs and symptoms, so doctors and nurses should regularly assess patients during tapering of analgosedation with an IWS scoring tool, not only rely on individual judgements. A pharmacological treatment algorithm may prevent IWS because then a step-by-step guide may contribute strategies for prevention and treatment of IWS. In our opinion, there is an urgent need for testing of weaning algorithms in PICUs. An algorithm can provide a common and predictable opioid and benzodiazepine tapering regime that does not depend on staff continuity. An algorithm needs to be developed that is easy to follow for all healthcare professionals, offering a safe and systematic approach when tapering analgosedation in PICU.

### 5 LIMITATIONS

Several limitations in the present study need to be addressed. First, we had a small sample size, the children had a wide range of diagnoses, and they were treated with different types of analgosedation. Second, regarding the use of WAT-1, the study group (five healthcare professionals) discussed how to score the children and all positive scores that could cause bias were removed; eg, if the child had loose stools due to clostridium or fever due to an infection. However, we were not able to test the interrater reliability between paired assessment scores. The questionnaire, developed to identify signs or symptoms that led to administration of additional bolus doses of analgesics or sedatives, was not validated and in some cases the nurses documented several symptoms as the cause of one bolus. This information was clarified with the nurses later, which presented a challenge because some symptoms could not be separated to justify one additional bolus.

### 6 CONCLUSION

This study demonstrated a very high prevalence of IWS in children exposed to long lasting infusions of opioids and benzodiazepines in PICUs without a written protocol for tapering of analgosedation, and not using any validated IWS monitoring tool. Additional bolus medication administered was primarily not an opioid, and this might have contributed to the high prevalence of IWS. Implementation and testing of weaning protocols are needed.

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CONFLICT OF INTEREST
The authors have no conflicts of interest.

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