Title

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Journal

Pediatric Critical Care Medicine, 17(1)

ISSN

1529-7535

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Publication Date

2016

DOI

10.1097/PCC.0000000000000572

Peer reviewed

Patterns of Sedation Weaning in Critically Ill Children Recovering From Acute Respiratory Failure*

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Objective: To characterize sedation weaning patterns in typical practice settings among children recovering from critical illness.

Design: A descriptive secondary analysis of data that were prospectively collected during the prerandomization phase (January to July 2009) of a clinical trial of sedation management.

Setting: Twenty-two PICUs across the United States.

Patients: The sample included 145 patients, aged 2 weeks to 17 years, mechanically ventilated for acute respiratory failure who received at least five consecutive days of opioid exposure.

Interventions: None.

Measurements and Main Results: 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. Demographic and clinical characteristics, tolerance to sedatives, and iatrogenic withdrawal symptoms were evaluated. Sixty-six patients (46%) were intermittently weaned; 79 patients were steadily weaned. Prior to weaning, intermittently weaned patients received higher peak and cumulative doses and longer exposures to opioids and benzodiazepines, demonstrated more sedative tolerance (58% vs 41%), and received more chloral hydrate and barbiturates compared with steadily weaned patients. During weaning, intermittently weaned patients assessed for withdrawal had a higher incidence of Withdrawal Assessment Tool-version 1 scores of greater than or equal to 3 (85% vs 46%) and received more sedative classes compared with steadily weaned patients.

Conclusions: This study characterizes sedative administration practices for pediatric patients prior to and during weaning from sedation after critical illness. It provides a novel methodology for describing weaning in an at-risk pediatric population that may be helpful in future research on weaning strategies to prevent iatrogenic withdrawal syndrome. (*Pediatr Crit Care Med* 2016; 17:19–29)

Key Words: benzodiazepine; opioid; Randomized Evaluation of Sedation Titration for Respiratory Failure; sedation; weaning; withdrawal assessment; Withdrawal Assessment Tool-version 1

***See also p. 87.**

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Members of the Randomized Evaluation of Sedation Titration for Respiratory Failure Baseline Study Investigators are listed in the *Acknowledgments* section.

All phases of data collection in the Randomized Evaluation of Sedation Titration for Respiratory Failure study were supported by grant HL086622/HL086649 from the National Institutes of Health.

Dr. Best was supported by a National Institutes of Health (NIH) grant #F31NR015172, and acknowledges funding from the Hillman Scholars Foundation. Her institution received grant support from the NHLBI and from the NINR (National Research Service Award [F31] to fund dissertation work). Dr. Asaro is employed by Boston Children's Hospital and received grant support and support for article research from the NIH. Her institution received grant support from the NIH. Dr. Franck received support for article research from the NIH. Her institution received grant support from the NIH (HL086622/HL086649). Dr. Wypij received support for article research from the NIH. Dr. Wypij and his institution received grant support from the NIH. Dr. Curley received support for article research from the NIH. Her institution received grant support from the NHLBI.

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DOI: 10.1097/PCC.0000000000000572

Most children supported on mechanical ventilation in the PICU receive opioids and benzodiazepines for sedation during the critical phase of their illness. Sedation is necessary to help the child mitigate the noxious effects of invasive therapies (1, 2). An estimated 16–35% of mechanically ventilated children become tolerant to sedative medications while in the PICU (3), defined as diminishing clinical effectiveness of a drug over the course of treatment (4, 5). However, as children recover from critical illness, sedative medications are discontinued or weaned over time. The amount of time spent weaning is a balance between keeping a

child comfortable and free from significant withdrawal symptoms that can complicate recovery and minimizing PICU and hospital lengths of stay (5, 6). Abrupt discontinuation or too rapid weaning of opioids and/or benzodiazepines in physically dependent children results in iatrogenic withdrawal syndrome (IWS), a cluster of physiologic signs and symptoms that includes nervous system hyperirritability, autonomic system dysregulation, gastrointestinal dysfunction, and motor abnormalities (4, 5, 7, 8).

The evidence informing optimal weaning practices is not robust (1, 9). It is known that children experiencing longer durations of sedative therapy (> 5 to > 9 d opioids [10, 11]; > 5 d benzodiazepines [12]) and higher cumulative doses (> 1.2 to > 2.5 mg/kg fentanyl [6, 10, 11, 13]; > 60 mg/kg midazolam [14]) are more likely to become tolerant (3, 13) and experience IWS (6, 10, 11, 13), which may necessitate a longer duration of weaning (4, 8). However, data on patient risk for protracted weaning and IWS are more than a decade old, and the distinction between preweaning and cumulative sedative exposure is often unclear. Nevertheless, current recommendations for sedation weaning include decreasing total doses by 10–20% every 24–48 hours as tolerated by the patient and/or sedation substitution with long-acting formulations (4, 15). Published reports of sedative tapering often exceed these rates (16) with an unclear sequence of opioid and/or benzodiazepine dose tapering (12, 15). Protocols using methadone weaning regimens can be problematic because of variable implementation and patient response (17, 18). Other sedative medications, such as dexmedetomidine, clonidine, and ketamine, have been introduced, but their contribution to successful weaning is unknown.

Given that there are now more sedative agents and nuanced approaches to sedation therapy, it is worth re-examining our understanding of which patients can or cannot tolerate rapid weaning, especially since the optimal approach to sedative titration remains elusive. Furthermore, the pattern and time course of opioid and benzodiazepine weaning in children recovering from critical illness remains poorly characterized. Clinician approaches to weaning may vary substantially (16) even in the presence of standardized sedation protocols. Greater understanding of the different patterns of weaning and their association with specific patient characteristics, such as clinical signs of IWS, may expedite the weaning process in at-risk patients. The purpose of this study was to characterize patterns of weaning in the context of current practice and to compare the characteristics of children with different patterns of weaning during recovery from critical illness.

MATERIALS AND METHODS

Design

This study was a secondary analysis conducted on prospective data from the baseline, prerandomization phase of the Randomized Evaluation of Sedation Titration fOr Respiratory FailurE (RESTORE) clinical trial. RESTORE was a multicenter study designed to test a sedation management protocol in critically ill pediatric patients with acute respiratory failure, defined as acute lung disease involving the airway and/or lung parenchyma (19). During the baseline, prerandomization phase (January–July 2009), all enrolled patients received usual care in 22 participating centers, but each PICU implemented the same pediatric-specific assessment tools for pain (i.e., depending on patient age, the Faces, Legs, Activity, Cry and Consolability, Wong-Baker Faces, Numeric Rating or Individualized Numeric Rating Scales), sedation (i.e., the State Behavior Scale or Assumed Agitation Present/Assumed Pain Present for neuromuscular blockade patients), and IWS (i.e., the Withdrawal Assessment Tool-version 1 [WAT-1]) (20, 21). Sedation management was otherwise unrestricted. Institutional review board approval was obtained from each participating site. Consent for data collection was provided by the parents and/or legal guardians of each patient.

Study Population

Patients aged 2 weeks (≥ 42 wk postmenstrual age) to 17 years were included if they were intubated and mechanically ventilated for acute respiratory failure (19). This analysis was restricted to baseline phase patients exposed to at least five consecutive days of opioids from continuous infusions, scheduled intermittent, or as needed bolus doses; who completed opioid weaning within the 28-day data collection period without transfer or redirection of care; and who survived to hospital discharge. This restriction allowed for the full evaluation of a patient's completed course of sedation therapy and the identification of individual patient patterns of weaning from sedation.

Variables and Measures

Demographic and clinical data collected at enrollment included patient age, gender, race, ethnicity, Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) (22), baseline verbal ability, mortality risk (Pediatric Risk of Mortality [PRISM] III-12) (23), reason for intubation, pediatric acute respiratory distress syndrome (PARDS) criteria (24), and medical history. The PCPC and the POPC are measures developed to describe cognitive impairment and functional morbidity in children, respectively (25). Each measure is a six-point scale of increasing disability ranging from normal function to death (22, 25). The PRISM III-12 score is a third-generation tool for estimating risk of PICU mortality based on a patient's age, operative status, and values for 17 physiologic variables measured within the first 12 hours after PICU admission (23). Higher scores indicate greater physiologic instability and higher risk of mortality. PARDS classifications were defined according to published criteria from the Pediatric Acute Lung Injury Consensus Conference Group (24). Hospital course variables included lengths of mechanical ventilation, PICU stay, and hospital stay.

Medication data included receipt of neuromuscular blockade, cumulative and peak daily opioid dosage (in morphine equivalents per kg of body weight), cumulative and peak daily benzodiazepine dosage collected to the end of opioid weaning (in midazolam equivalents per kg of body weight), and administration of any other sedative medications (e.g.,

chloral hydrate, clonidine, dexmedetomidine, ketamine, pentobarbital, phenobarbital, and propofol). Daily and cumulative sedative medication doses were compared using standard equivalencies. Specifically, morphine equivalent conversion factors to equal 1 mg morphine sulfate were as follows: 15 µg remifentanil, 15 µg fentanyl, 0.15 mg hydromorphone, and 0.3 mg methadone (19). Midazolam equivalent conversion factors to equal 1 mg midazolam were 0.2 mg clonazepam, 0.3 mg lorazepam, and 2 mg diazepam (19). Sedative data were collected daily from endotracheal intubation, initiation of assisted breathing for patients with tracheostomies, or PICU admission for patients intubated at an outside hospital (day 0) until 72 hours after their last opioid dose, hospital discharge, or day 28 (whichever occurred first). Thresholds for opioid and benzodiazepine exposure from previous investigations of IWS, such as more than 60 mg/kg of midazolam (14), were examined (6, 11, 13). Tolerance to the sedative effect of opioids was defined as a doubling of the day 2 opioid dose prior to the start of weaning, an adaptation of Anand et al (3) who defined tolerance as a doubling of the initially effective dose received during the first 24 hours of therapy. Using day 2 data provided a more conservative approach to quantifying tolerance in cases where subjects may have been started on suboptimal initial doses and required titration to achieve clinical effect. This definition was also adapted to describe benzodiazepine tolerance, that is, doubling of the day 2 benzodiazepine dose prior to opioid weaning, since a comparable reference for benzodiazepines is not available in the current literature.

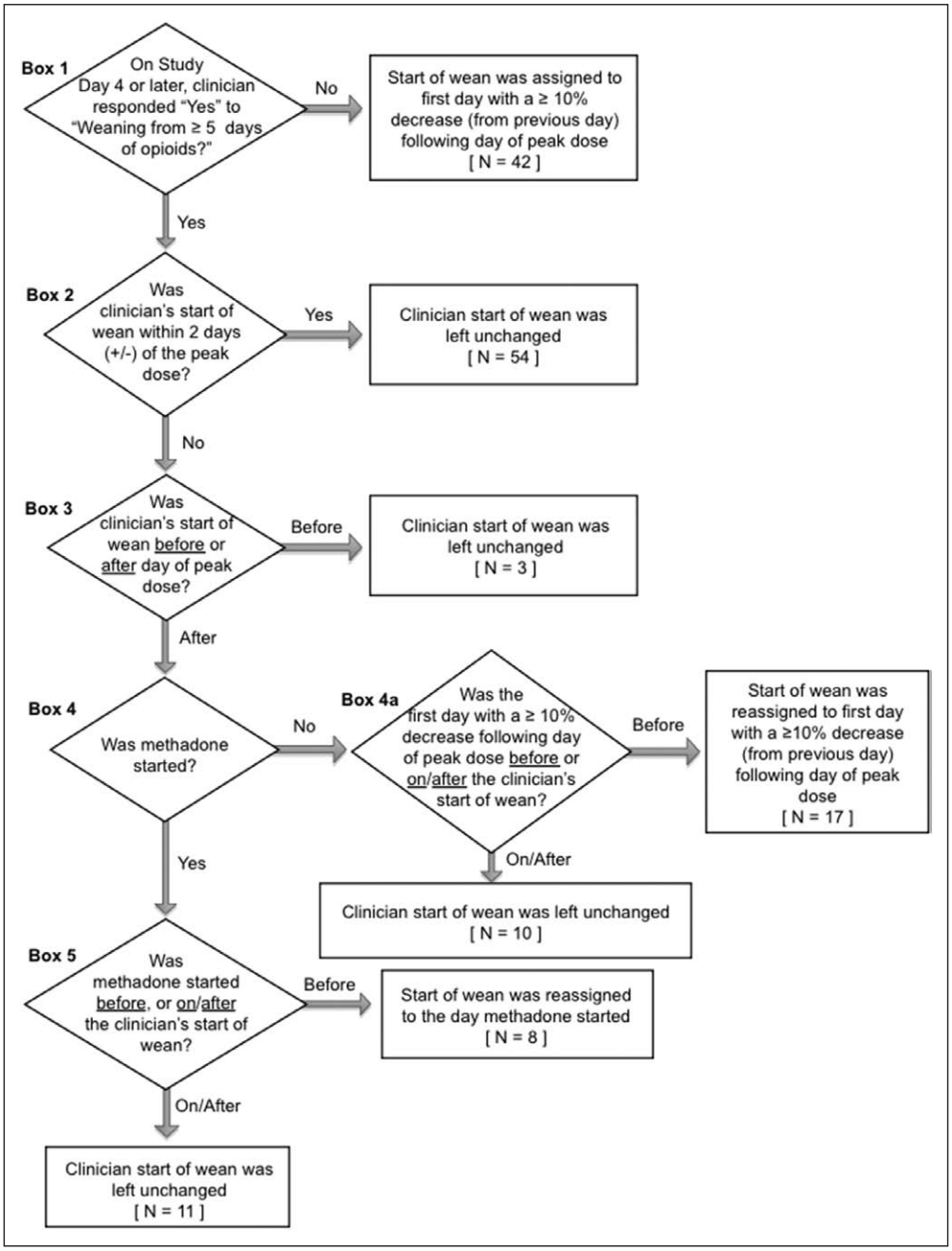

Figure 1. Start of weaning decision algorithm. Note: The algorithm assigned the start of opioid weaning for 42 patients (29%) missing data on the clinician-reported start of weaning. For the remaining 103 patients, the clinician-reported start of weaning was verified by the algorithm for 78 patients (76%) and reassigned for 25 patients (24%).

Patients were assessed for signs of IWS using the WAT-1 (20, 26). The WAT-1 is an 11-item (12-point) instrument that includes a review of the patient's medical record for the past 12 hours; direct observation of the patient for 2 minutes prestimulation; patient response to stimulation (27); and assessment of poststimulus recovery (26). WAT-1 scoring was to be completed at least every 12 hours while the patient was in the PICU and at least daily while in the hospital, from the day opioid weaning commenced until 72 hours after the patient received the last opioid dose. The highest daily WAT-1 score was used in analyses, with scores of greater than or equal to 3 being used as a validated cutoff for IWS from previous studies (20, 26). No recommendations were provided for patient management based on WAT-1 score during the baseline phase, and individual clinicians at each site determined the course of treatment according to usual practice.

Weaning Pattern

Line graphs illustrating daily opioid and benzodiazepine

doses and WAT-1 scores over the study period were constructed for each patient (L.A.A). Two investigators (L.S.F., M.A.Q.C.), blind to the clinical characteristics of each patient, independently reviewed each patient's graph to make a preliminary determination regarding each patient's weaning pattern. These observations were then used to construct a decision-making algorithm (K.M.B.) for verifying, assigning, or reassigning the patient's clinician-reported start of opioid weaning (**Fig. 1**). Assignment of the start of opioid weaning was necessary for patients with missing data. In addition, the clinician-reported start of opioid weaning may have been unreliable in cases where there was more than a 2-day difference between the start of weaning and the day of peak dose. The start of opioid weaning was reassigned if 1) the clinician-reported start of weaning occurred more than 2 days after a peak opioid dose that was accompanied by 10% or greater dose decrease and/or 2) methadone was started more than 2 days before the clinician-reported start of weaning. We maintained clinician-reported starts of weaning occurring more than 2 days before the day of peak dose assuming that the patient experienced a difficult course of weaning leading to bolus dosing and a later peak.

Once a patient's start of weaning was verified, a weaning pattern was assigned. An intermittent pattern of weaning was assigned to those patients with an irregular pattern of sedative administration during weaning that included a 20% or greater increase in the total daily opioid dose at any time during the weaning period. A steady pattern of weaning was assigned to the remaining patients.

Data Analysis

Descriptive statistics were calculated, including means, SDs, medians, and interquartile ranges (IQRs) for continuous variables and frequency counts and percentages for categorical variables. Group comparisons were made between patients with an intermittent weaning pattern and those with a steady weaning pattern. Logistic, cumulative logit, linear, and proportional hazards regression, accounting for PICU as a cluster variable using generalized estimating equations, were used to analyze binary, ordinal, log-transformed continuous, and time-to-event variables, respectively. Analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 3.1.1; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Of 308 patients enrolled in the baseline, prerandomization phase of the RESTORE clinical trial, 186 patients experienced five or more consecutive days of opioid administration. An additional 41 patients were excluded: 36 patients for whom weaning was not complete by the end of the 28-day study period, one patient who was lost to follow-up because of transfer to an outside institution, and four nonsurvivors. The final sample included 145 patients.

The median opioid start of weaning was 6 days (IQR, 5–8 d), and 66 patients (46%) were intermittently weaned. The start of opioid weaning occurred later for patients with an intermittent pattern of weaning compared with patients with a steady pattern of weaning (median, day 6; IQR, 5–9 vs day 5; 5–7; $p = 0.006$). **Figure 2** illustrates graphs of representative patients with intermittent and steady patterns of weaning.

Patient characteristics are shown in **Table 1**. There were no significant differences in baseline demographic or clinical

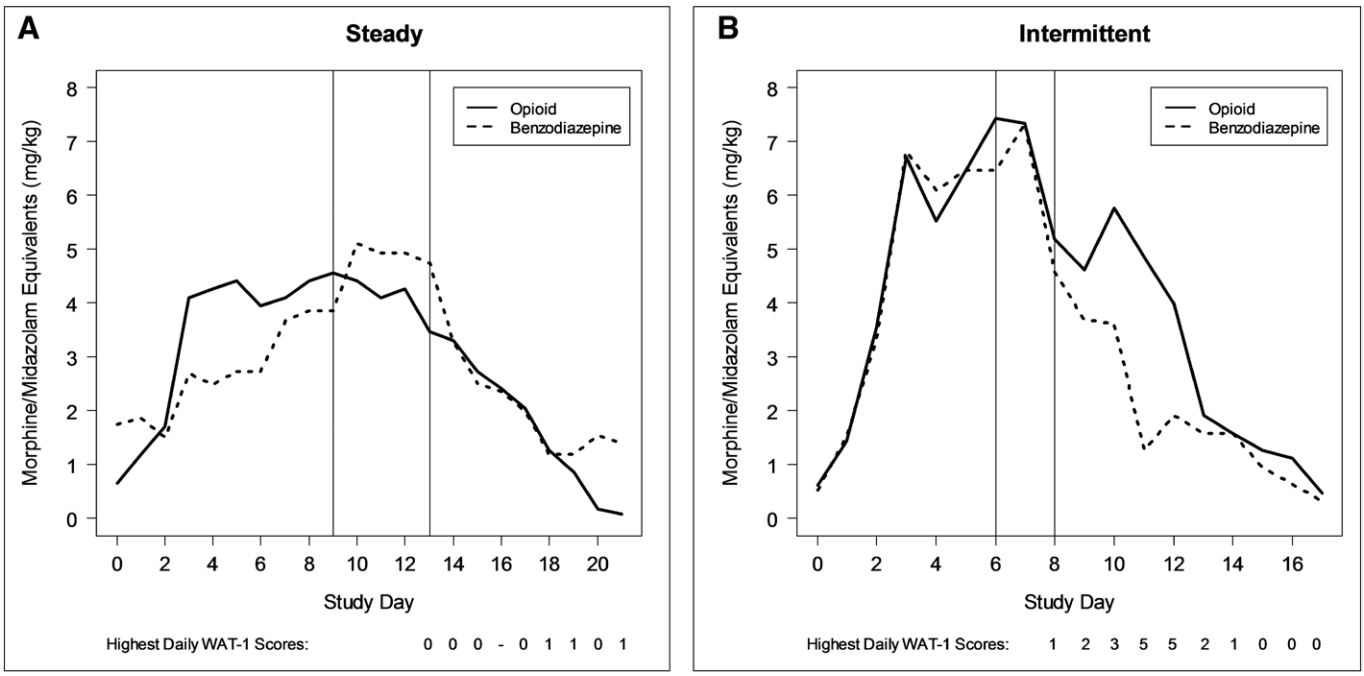

Figure 2. Opioid weaning patterns. Representative graphs of daily opioid and benzodiazepine doses among patients with steady (**A**) and intermittent (**B**) patterns of opioid weaning. Note: The *first vertical line* marks the day of the peak opioid dose, while the *second vertical line* represents the start of the opioid weaning period.

TABLE 1. Patient Characteristics by Pattern of Weaning

Variable	Steady Wean (*n* = 79)	Intermittent Wean (*n* = 66)	*p*[a]
Baseline characteristics			
Age at PICU admission			
Median (IQR), yr	2.0 (0.4–8.3)	1.4 (0.3–4.9)	0.32
2 wk to 1.99 yr, *n* (%)	40 (51)	37 (56)	0.16
2.00 yr to 5.99 yr, *n* (%)	11 (14)	15 (23)	
6.00 yr to 17.99 yr, *n* (%)	28 (35)	14 (21)	
Female, *n* (%)	45 (57)	33 (50)	0.49
Non-Hispanic white, *n*/total *n* (%)	45/76 (59)	43/64 (67)	0.52
Baseline Pediatric Cerebral Performance Category = 1, *n* (%)[b]	62 (78)	48 (73)	0.28
Baseline Pediatric Overall Performance Category = 1, *n* (%)[b]	61 (77)	45 (68)	0.11
Able to verbally communicate pain at baseline, *n*/total *n* (%)[c]	31/44 (70)	29/34 (85)	< 0.001
PRISM III-12 score, median (IQR)	6 (2–12)	6 (3–12)	0.44
Percent risk of mortality based on PRISM III-12 score, median (IQR)	2 (1–12)	3 (1–13)	0.46
Primary reason for intubation, *n* (%)			0.58
Pneumonia	31 (39)	28 (42)	
Bronchiolitis	23 (29)	16 (24)	
Acute respiratory failure related to sepsis	6 (8)	7 (11)	
Asthma or reactive airway disease	5 (6)	5 (8)	
Aspiration pneumonia	4 (5)	1 (2)	
Other	10 (13)	9 (14)	
Pediatric acute respiratory distress syndrome based on day 1 OI or OSI, *n* (%)[d]			0.76
At risk (OI, < 4.0 or OSI, < 5.0)	28 (35)	23 (35)	
Mild (OI, 4.0–7.9 or OSI, 5.0–7.4)	24 (30)	17 (26)	
Moderate (OI, 8.0–15.9 or OSI, 7.5–12.2)	18 (23)	19 (29)	
Severe (OI, ≥ 16.0 or OSI, ≥ 12.3)	9 (11)	7 (11)	
Neuromuscular blockade for the entire duration of days 0–2, *n* (%)	3 (4)	5 (8)	0.40
Any medical history, *n* (%)			
Prematurity (< 36 wk postmenstrual age)	10 (13)	5 (8)	0.14
Asthma (prescribed bronchodilators or steroids)	12 (15)	10 (15)	0.96
Seizure disorder (prescribed anticonvulsants)	11 (14)	6 (9)	0.46
Neurologic/neuromuscular disorder which places patient at risk for aspiration	8 (10)	7 (11)	0.83
Cancer (current or past diagnosis)	1 (1)	5 (8)	0.03
Known chromosomal abnormality	3 (4)	4 (6)	0.52

(*Continued*)

TABLE 1. (*Continued*). Patient Characteristics by Pattern of Weaning

Variable	Steady Wean ($n = 79$)	Intermittent Wean ($n = 66$)	p[a]
Hospital course, d, median (IQR)			
Duration of mechanical ventilation	5.9 (4.7–8.2)	9.1 (6.3–11.9)	< 0.001
PICU length of stay	9.3 (6.9–12.7)	12.8 (9.5–17.0)	< 0.001
Hospital length of stay	14 (10–20)	21.5 (16–26)	< 0.001

IQR = interquartile range, PRISM III-12 = Pediatric Risk of Mortality III score from first 12 hr in the PICU, OI = oxygenation index, OSI = oxygen saturation index.

[a]*p* values for the comparison of patients with steady versus intermittent weaning patterns were calculated using linear, cumulative logit, logistic, and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, ordinal, binary, and time-to-event variables, respectively.

[b]Pediatric Cerebral Performance Category and Pediatric Overall Performance Category range from 1 to 6, with higher categories indicating greater impairment.

[c]Able to verbally communicate pain at baseline includes only patients aged 16 mo and older.

[d]OI was calculated as [(Fio_2 × mean airway pressure)/Pao_2 × 100]. When an arterial blood gas was not available, Spo_2 was used to estimate Pao_2 to calculate OSI [(Fio_2 × mean airway pressure)/Spo_2 × 100]. Lower scores reflect better oxygenation.

characteristics between patients with intermittent and steady patterns of weaning, aside from more patients able to verbally communicate pain at baseline or with a history of cancer in the intermittently weaned group. Patients with an intermittent pattern of weaning experienced longer durations of mechanical ventilation and PICU and hospital lengths of stay when compared with patients who were weaned steadily. Patients with an intermittent pattern of weaning also had higher total cumulative opioid (median, 35.7 mg/kg; IQR, 17.4–61.2 vs 16.5 mg/kg; 7.4–25.5; $p < 0.001$) and benzodiazepine (28.3 mg/kg; 11.2–65.0 vs 12.8 mg/kg; 5.7–22.2; $p < 0.001$) doses than patients with a steady pattern of weaning.

Preweaning Exposure

Characteristics of opioid and benzodiazepine exposure in the preweaning period are shown in **Table 2**. The majority of patients in both groups received fentanyl and midazolam as their primary opioid and benzodiazepine agents. In the preweaning period, patients with an intermittent pattern of weaning received higher preweaning daily peak and cumulative doses of opioids and benzodiazepines and had longer durations of exposure to opioids and benzodiazepines. Patients with an intermittent weaning pattern were also more likely to have developed tolerance to either opioids or benzodiazepines and to have received a total midazolam dose more than 60 mg/kg prior to the start of weaning. Intermittently weaned patients were more likely to have received chloral hydrate and barbiturates. There were no significant differences between groups in the number of patients receiving methadone, clonidine, dexmedetomidine, ketamine, or propofol prior to the start of opioid weaning.

Exposure During Weaning

Characteristics of opioid and benzodiazepine exposure during weaning are shown in **Table 3**. The percent decrease in daily opioid dose over the first 24 and 48 hours after the initiation of weaning was lower among patients with intermittent patterns of weaning. A similar pattern was observed in the percent decrease in daily benzodiazepine dose over the first 48 hours of opioid weaning. Intermittently weaned patients received more opioid and benzodiazepine boluses and received boluses for significantly more days during the weaning period. A greater proportion of patients with an intermittent pattern of weaning received methadone, clonidine, dexmedetomidine, chloral hydrate, and barbiturates during the weaning period.

Associations With IWS

One hundred twelve patients (77%) were assessed for withdrawal symptoms using the WAT-1. There were no significant differences in demographic characteristics between patients who were or were not assessed, although patients without assessments received lower preweaning cumulative opioid (median, 11.0 mg/kg; IQR, 3.6–19.9 vs 17.8 mg/kg; 9.2–29.2; $p = 0.01$) and benzodiazepine (median, 7.1 mg/kg; IQR, 2.6–14.9 vs 14.1 mg/kg; 6.2–26.2; $p = 0.01$) doses. More patients with an intermittent pattern of weaning had WAT-1 assessments performed during the weaning period, had WAT-1 scores of greater than or equal to 3, and had higher peak WAT-1 scores (**Table 3**). The first WAT-1 score of greater than or equal to 3 was observed within the first 48 hours of opioid weaning in 61% of patients (46/76). Among patients with WAT-1 assessments, tolerance to either opioids or benzodiazepines was observed more frequently in patients who ever had WAT-1 scores of greater than or equal to 3, compared with patients who always scored less than 3 (57% vs 33%; $p = 0.01$).

DISCUSSION

This study is the first multicenter analysis of patterns of sedation weaning among children recovering from critical illness. We used a novel algorithm to identify the start of weaning with a graphical approach to plot changes in sedative dosing with corresponding withdrawal assessments for each patient, which allowed us to classify two patterns of weaning: intermittent and steady. The intermittent weaning pattern was associated with higher (preweaning and overall) cumulative and peak doses and longer preweaning exposures of opioids and benzodiazepines, as well as longer lengths of hospital stay. Higher WAT-1 scores associated with IWS were also seen in intermittently weaned patients with completed assessments. In contrast, steadily weaned patients tolerated rapid decreases in both opioid and benzodiazepine doses with a lower incidence of IWS; some patients were

TABLE 2. Opioid and Benzodiazepine Exposure Preopioid Weaning by Pattern of Weaning

Variable	Steady Wean (*n* = 79)	Intermittent Wean (*n* = 66)	*p*[a]
Primary opioid agent preweaning, *n* (%)[b]			0.94[c]
Fentanyl	58 (73)	47 (71)	
Morphine	21 (27)	18 (27)	
Hydromorphone	0	1 (2)	
Opioid exposure preweaning, mg/kg, median (IQR)[d]			
Peak daily dose	3.4 (1.7–5.7)	5.0 (2.6–7.9)	0.006
Cumulative dose	13.4 (6.4–21.7)	19.8 (9.7–39.1)	0.004
Cumulative dose—morphine only	0.1 (0–1.3)	0.4 (0–2.6)	0.04
Cumulative dose—fentanyl only, μg/kg	187.8 (3.1–319.0)	196.7 (16.2–433.4)	0.30
Exposure days—median (IQR)	5 (5–6)	6 (5–9)	< 0.001
Primary benzodiazepine agent preopioid weaning, *n* (%)[b,e]			0.52[f]
Midazolam	59 (75)	51 (77)	
Lorazepam	18 (23)	15 (23)	
None	2 (3)	0	
Benzodiazepine exposure preopioid weaning, mg/kg, median (IQR)[e]			
Peak daily dose	2.7 (1.5–4.9)	4.1 (1.6–7.3)	0.005
Cumulative dose	9.6 (4.6–17.6)	15.4 (6.1–38.5)	< 0.001
Exposure days	5 (5–6)	6 (5–9)	< 0.001
Tolerance, *n* (%)			
Doubling of day 2 opioid dose preopioid weaning	19 (24)	26 (39)	0.01
Doubling of day 2 benzodiazepine dose preopioid weaning	24 (30)	28 (42)	0.14
Doubling of day 2 opioid dose or day 2 benzodiazepine dose preopioid weaning	32 (41)	38 (58)	0.03
Thresholds preopioid weaning, *n* (%)			
Total fentanyl > 2.5 mg/kg or > 9 d (11)	6 (8)	9 (14)	0.33
Total fentanyl > 1.6 mg/kg or > 5 d (12)	23 (29)	27 (41)	0.14
Total fentanyl > 1.2 mg/kg (6)	0	4 (6)	0.27
Total midazolam > 60 mg/kg[e] (14)	0	11 (17)	0.005
Other sedatives preopioid weaning, *n* (%)			
Methadone	6 (8)	10 (15)	0.09
Clonidine	0	1 (2)	1.0
Dexmedetomidine	12 (15)	16 (24)	0.17
Ketamine	11 (14)	10 (15)	0.92
Chloral hydrate	7 (9)	14 (21)	0.01
Propofol	10 (13)	3 (5)	0.11
Barbiturates	3 (4)	9 (14)	0.04

(*Continued*)

TABLE 2. (*Continued*). Opioid and Benzodiazepine Exposure Preopioid Weaning by Pattern of Weaning

Variable	Steady Wean (*n* = 79)	Intermittent Wean (*n* = 66)	*p*[a]
No. of sedative classes received preopioid weaning, median (IQR)[g]	2 (2–3)	2 (2–3)	0.07
1, *n* (%)	2 (3)	0	
2, *n* (%)	46 (58)	34 (52)	
3, *n* (%)	22 (28)	18 (27)	
4–7, *n* (%)	9 (11)	14 (21)	

IQR, interquartile range.

[a]*p* values for the comparison of patients with steady versus intermittent weaning patterns were calculated using logistic, linear, and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for binary, log-transformed continuous, and time-to-event variables, respectively. Where there was a zero count in the steady wean group, the *p* value was calculated with the use of a stratified exact test with adjustment for site.

[b]Primary opioid agent during the preweaning period was defined as the opioid administered via continuous infusion. If no opioid or more than one opioid was administered via continuous infusion, primary opioid agent was defined as the opioid administered on the highest number of study days. If fentanyl and morphine were administered on the same number of days, primary opioid agent was defined as the opioid contributing the highest morphine equivalents. Primary benzodiazepine during the preopioid weaning period was assigned similarly. If midazolam and lorazepam were administered on the same number of days, primary benzodiazepine agent was defined as the benzodiazepine contributing the highest midazolam equivalents.

[c]This *p* value compares primary agent morphine versus fentanyl.

[d]Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanil (0.015).

[e]Benzodiazepine data were collected until study discharge, which was based on the end of opioid exposure; thus, patients may have still been receiving benzodiazepines at study discharge. Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

[f]This *p* value compares primary agent midazolam versus lorazepam.

[g]Different sedative classes include opioids, benzodiazepines, α2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.

completely weaned from sedation within 48 hours. From these findings, it appears possible that certain patient groups with less complicated preweaning sedation courses can be weaned more quickly even than published recommendations. Meanwhile, standardized protocols involving slower courses of weaning and/or more proactive approaches to preventing IWS could benefit patients who would otherwise be intermittently weaned, with important implications for impacting lengths of stay.

Our findings align with previous research, which showed that higher cumulative and peak doses of opioids and benzodiazepines and longer exposures are associated with IWS (6, 10–13, 16, 20, 28). However, our data are the first to quantify their associations with an intermittent weaning pattern. While intuitive, these findings suggest that current weaning practices should be more critically examined not only for the rate of dose reductions but also for consistency. Of note, our two patterns of weaning could not be differentiated by previously published threshold doses of fentanyl that have been associated with IWS. These published thresholds included sedative doses received after the start of weaning (6, 10, 11), a criterion that limits their prognostic utility for weaning outcomes. Nevertheless, more intermittently weaned patients exceeded threshold doses of midazolam (14) in the preopioid weaning period. When considered in the context of the additional finding that nearly half of patients in this study met criteria for tolerance to either opioids or benzodiazepines, it appears that benzodiazepines ought to receive more consideration during weaning. Specifically, the common practice of concurrently weaning opioids and benzodiazepines may be problematic when physical dependence on one or both medications is probable and should be prospectively compared with gradual withdrawal of one sedative class at a time. We also agree with Anand et al (3) that efforts to reduce prolonged sedative exposure for children in the PICU should be pursued.

This study extended a previous definition of opioid tolerance (3) to include benzodiazepines and is the first to identify associations with weaning and other clinical outcomes. Typically, the focus in quantifying tolerance has been placed on the escalation of sedation therapy and not necessarily on sedation weaning. Future studies can apply this easily computed definition of tolerance, that is, a doubling of the day 2 sedative dose to achieve the same therapeutic effect over the acute preweaning phase of illness, when examining sedative administration practices. However, further validation studies should be conducted and linked to prospective evaluation of sedative administration and subsequent patterns of weaning. Clinicians may also find these definitions of tolerance helpful when planning how best to wean patients from sedation.

Our data show wide variation in the percent drop in either opioid or benzodiazepine dose experienced by patients during opioid weaning. In part, this may be explained by the fact that patients with an intermittent pattern of weaning received significantly more opioid and benzodiazepine rescue bolus doses for a greater number of days during the weaning period, beginning with the day of the start of opioid weaning. This result may indicate that signs of IWS were first observed soon after the start of weaning, as suggested by the finding that the majority of patients with WAT-1 scores of greater than or equal to 3 were identified within the first 48 hours of opioid weaning. Examination of WAT-1 scores showed that more intermittently weaned patients with assessments had peak WAT-1 scores of

TABLE 3. Opioid and Benzodiazepine Exposure During Opioid Weaning by Pattern of Weaning

Variable	Steady Wean (*n* = 79)	Intermittent Wean (*n* = 66)	*p*[a]
Opioid exposure during weaning, mg/kg, median (IQR)			
Peak daily dose[b]	0.9 (0.1–2.7)	3.0 (1.0–5.6)	< 0.001
Cumulative dose[b]	1.5 (0.1–4.3)	11.5 (3.9–19.9)	< 0.001
Exposure days, median (IQR)	2 (1–5)	10.5 (8–13)	< 0.001
Benzodiazepine exposure during opioid weaning, mg/kg, median (IQR)			
Peak daily dose[c]	1.1 (0.1–2.6)	2.3 (1.2–5.5)	< 0.001
Cumulative dose[c]	1.5 (0.3–4.5)	9.0 (2.7–19.6)	< 0.001
Percent drop in daily opioid dose from start of wean to next day, median (IQR)[d]	47 (0–100)	24 (–10 to 57)	< 0.001
Percent drop in daily opioid dose from start of wean to 2 d later, median (IQR)[d]	82 (13–100)	42 (–2 to 81)	0.02
Percent drop in daily benzodiazepine dose from start of opioid wean to next day, median (IQR)[d]	28 (0–98)	32 (0–61)	0.10
Percent drop in daily benzodiazepine dose from start of opioid wean to 2 d later, median (IQR)[d]	63 (0–100)	48 (0–75)	0.002
Received opioid bolus doses during weaning, *n* (%)	50 (63)	57 (86)	0.003
No. of days patient received opioid bolus doses, median (IQR)	1 (1–2)	3 (2–5)	< 0.001
Received benzodiazepine bolus doses during opioid weaning, *n* (%)	49 (62)	56 (85)	0.02
No. of days patient received benzodiazepine bolus doses, median (IQR)	2 (1–3)	3 (1.5–4)	0.001
Other sedatives during opioid weaning, *n* (%)[e]			
Methadone	15 (19)	37 (56)	< 0.001
Clonidine	1 (1)	8 (12)	0.004
Dexmedetomidine	14 (18)	23 (35)	0.002
Ketamine	4 (5)	5 (8)	0.64
Chloral hydrate	3 (4)	7 (11)	0.04
Propofol	6 (8)	7 (11)	0.64
Barbiturates	2 (3)	6 (9)	0.002
No. of sedative classes received during opioid weaning, median (IQR)	2 (1–3)	2 (2–3)	< 0.001
0, *n* (%)	7 (9)	0	
1, *n* (%)	13 (16)	4 (6)	
2, *n* (%)	39 (49)	31 (47)	
3, *n* (%)	14 (18)	16 (24)	
4–7, *n* (%)	6 (8)	15 (23)	

(*Continued*)

TABLE 3. (*Continued*). Opioid and Benzodiazepine Exposure During Opioid Weaning by Pattern of Weaning

Variable	Steady Wean (*n* = 79)	Intermittent Wean (*n* = 66)	*p*[a]
WAT-1 assessments performed during opioid weaning, *n* (%)	50 (63)	62 (94)	< 0.001
WAT-1 ever ≥ 3, *n*/total *n* (%)	23/50 (46)	53/62 (85)	< 0.001
Peak WAT-1 score, median (IQR)	2 (1–5)	5 (4–6)	< 0.001

IQR = interquartile range, WAT-1 = Withdrawal Assessment Tool-version 1.

[a]*p* values for the comparison of patients with steady versus intermittent weaning patterns were calculated using linear, proportional hazards, and logistic regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, time-to-event, and binary variables, respectively. Percent drop variables were not log-transformed due to negative values.

[b]Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanil (0.015).

[c]Benzodiazepine data were collected until study discharge, which was based on the end of opioid exposure; thus, patients may have still been receiving benzodiazepines at study discharge. Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

[d]Excludes two steadily weaned patients who started weaning on day 5 and were study discharged that day.

[e]Different sedative classes include opioids, benzodiazepines, α2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.

greater than or equal to 3. It is interesting to note that patients with intermittent patterns of weaning experienced greater frequency and severity of WAT-1 scores despite receiving significantly more doses of methadone, clonidine, dexmedetomidine, chloral hydrate, and barbiturates during the weaning period. Additional work is needed both to help reduce preweaning sedative exposures in patients who may be difficult to sedate and to ease the transition into sedative weaning for those at risk for intermittent weaning. Close monitoring of patients undergoing weaning should aim to quickly identify and treat inconsistencies that may prolong weaning, induce IWS symptoms, and/or extend lengths of stay.

This study has some limitations, the most significant of which is that the findings cannot offer evidence for causation. The question of whether intermittent weaning patterns are the outcome of preweaning risk factors or a contributory cause of higher WAT-1 scores and more intensive or protracted weaning remains unanswered. In particular, our method of data collection made it difficult to identify patients who might have experienced increased sedative doses during weaning due to procedural sedation or changes in clinical condition. Not all patients were assessed for IWS, which may have caused an ascertainment bias in the observed association between intermittent weaning and IWS. Without a complete picture of benzodiazepine weaning in this dataset or a validated definition of benzodiazepine tolerance, conclusions about tolerance to benzodiazepines among patients in this study are only tentative. As in previous studies (7, 26), it is impossible to parse the effects of these medications, since most patients received both concurrently, but the start of benzodiazepine weaning should be examined to determine whether similar relationships exist. Finally, the available data offer little insight into the clinical practices or environment in which children were undergoing recovery and weaning or the effects of either sedation therapy or the environment on restorative sleep, both of which may have been contributory to increased sedative needs in certain patients (29, 30). These considerations will require further research.

CONCLUSIONS

This study provides further characterization of the clinical profiles of pediatric patients during weaning from sedatives after critical illness. Using baseline, preintervention data allowed this study an unrestrained view of current practices in sedation management and weaning in PICUs of varying size and geographic location. Our findings suggest that weaning is steady and uncomplicated among patients who receive lower preweaning medication doses and fewer days of sedative exposure. By contrast, intermittent weaning is associated with opioid tolerance and possibly worse clinical outcomes, including higher incidence and severity of withdrawal symptoms and longer lengths of stay. Further research is needed to improve the practice of opioid and benzodiazepine weaning in pediatric patients, which may be strengthened by the application of the methods and operational definitions described here.

ACKNOWLEDGMENTS

RESTORE Baseline Study Investigators include Geoffrey L. Allen (Children's Mercy Hospital, Kansas City, MO); Judy A. Ascenzi (The Johns Hopkins Hospital, Baltimore, MD); Scot T. Bateman (University of Massachusetts Memorial Children's Medical Center, Worcester, MA); Santiago Borasino (Children's Hospital of Alabama, Birmingham, AL); Ira M. Cheifetz (Duke Children's Hospital, Durham, NC); Allison S. Cowl (Connecticut Children's Medical Center, Hartford, CT); E. Vincent S. Faustino (Yale-New Haven Children's Hospital, New Haven, CT); Lori D. Fineman (University of California San Francisco Benioff Children's Hospital at San Francisco, San Francisco, CA); Heidi R. Flori (University of California at San Francisco Benioff Children's Hospital at Oakland, Oakland, CA); Mary Jo C. Grant (Primary Children's Hospital, Salt Lake City, UT); James H. Hertzog (Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE); Larissa Hutchins (The Children's Hospital of Philadelphia, Philadelphia, PA); Aileen L. Kirby

(Oregon Health & Science University Doernbecher Children's Hospital, Portland, OR); JoAnne E. Natale (University of California Davis Children's Hospital, Sacramento, CA); Phineas P. Oren (St. Louis Children's Hospital, St. Louis, MO); Nagendra Polavarapu (Advocate Children's Hospital-Oak Lawn, Oak Lawn, IL); Thomas P. Shanley (C. S. Mott Children's Hospital at the University of Michigan, Ann Arbor, MI); Shari Simone (University of Maryland Medical Center, Baltimore, MD); Lauren R. Sorce (Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL); Michele A. Vander Heyden (Children's Hospital at Dartmouth, Dartmouth, NH).

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