Exposure-Based Methadone and Lorazepam Weaning Protocol Reduces Wean Length in Children

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OBJECTIVE Determine if a standardized methadone and lorazepam weaning protocol that is based on dose and duration of exposure can reduce the length of opioid and benzodiazepine weaning and shorten hospital stay.

METHODS Retrospective cohort study performed in a 24-bed medical/surgical PICU. A total of 177 patients on opioid and/or benzodiazepine infusions for >3 days were included; 75 patients pre protocol (June 2012–June 2013) were compared with 102 patients post implementation of a standardized weaning protocol of methadone and lorazepam (March 2014–March 2015). The recommended wean was based on duration of infusions of >3 days up to 5 days (no wean), 5 to 13 days (short wean), and ≥14 days (long wean).

RESULTS Median number of days on methadone for patients on opioid infusions for 5 to 13 days was reduced from 8.5 to 5.7 days ($p = 0.001$; $n = 45$ [pre], $n = 68$ [post]) and for patients on opioid infusions for ≥14 days, from 29.7 to 11.5 days ($p = 0.003$; $n = 9$ [pre], $n = 9$ [post]) after protocol implementation. The median number of days on lorazepam for patients on benzodiazepine infusions for 5 to 13 days was reduced from 8.1 to 5.2 days ($p = 0.020$; $n = 43$ [pre], $n = 55$ [post]) and for patients on benzodiazepine infusions for ≥14 days, from 27.4 to 9.3 days ($p = 0.011$; $n = 9$ [pre], $n = 8$ [post]). There was no difference in methadone or lorazepam wean length for patients on 3 to 5 days of infusions. There was no difference in adverse events or hospital length of stay.

CONCLUSIONS A methadone and lorazepam weaning protocol based on patient's exposure to opioids and benzodiazepines (dose and duration) reduces weaning length.

ABBREVIATIONS IV, intravenous; LOS, length of stay; MAR, medication administration record; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality; WAT-1, Withdrawal Assessment Tool, version 1

KEYWORDS analgesia; benzodiazepines; clinical protocols; methadone; opioid; pediatrics; substance withdrawal syndrome

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Introduction

Children admitted to the PICU are frequently exposed to opioid and benzodiazepine infusions for analgesia and sedation.¹ Owing to the severity of illness of many children in the PICU, prolonged exposure to opioids and benzodiazepines frequently occurs, resulting in an increased risk of withdrawal when these medications are no longer required.^{2,3} To prevent iatrogenic withdrawal, these medications must be carefully tapered.

The symptoms of withdrawal, which may occur from abrupt discontinuation or tapering medications too quickly, include neurological excitability, gastrointestinal dysfunction, and autonomic dysfunction.^{4–6} These symptoms cause physiological and emotional distress for the patients and their family and can lead to prolongation of medication tapering and, potentially, LOS.^{7,8} Currently, significant practice variation exists within and between institutions with regard to the weaning of opioids and benzodiazepines.^{9,10} In the absence

of a standardized approach, patients are frequently treated at the discretion of the provider, which can lead to overtreatment or undertreatment of withdrawal.^{11–14}

Most of the pediatric literature has focused on the weaning of opioids with limited data on benzodiazepines even though many patients are treated concurrently with benzodiazepine and opioid infusions.^{11,12,14–16} In addition, although total exposure, including both duration of therapy and dose, is an important determinant of withdrawal risk for opioids^{4,8,9,17–19} and benzodiazepines,^{19,20} most weaning protocols have used a single dose and weaning schedule for all patients.²¹ Many times if exposure is considered in a protocol, only one of these factors, dose or duration, is used in designing the wean.^{11,14–16,22} Although several medications have been used to treat withdrawal symptoms, we selected methadone because of favorable characteristics including a long half-life, enteral route of administration, and familiarity, for the prevention of opioid withdrawal.

Similarly, lorazepam, with its longer half-life but without some of the drawbacks of diazepam, including active metabolites with variable half-lives,³ was selected for the prevention of benzodiazepine withdrawal. We hypothesized that the implementation of a standardized methadone and lorazepam weaning protocol based on both dose and duration of exposure of each medication would reduce the length of wean for opioids and benzodiazepines and decrease hospital LOS.

Materials and Methods

Study Design. This study was a retrospective review of the medical records of patients at risk of iatrogenic opioid and benzodiazepine withdrawal. This study was conducted at a free-standing, 204-bed children's hospital with a 24-bed mixed medical/surgical PICU. The study was approved by the Seton Healthcare Family Institutional Review Board and was exempt from the need for patient informed consent. Patients treated with opioid and benzodiazepine infusions for greater than 3 days in the PICU between June 2012 and June 2013 (pre protocol implementation) were compared with a group of patients admitted between March 2014 and March 2015 after the implementation of a standardized weaning protocol in June 2013 (post protocol implementation). The 3-day minimum was selected from our clinical experience with withdrawal symptoms in patients who received sedative/analgesic infusions for greater but not less than 3 days and is supported by research indicating a 20% risk of withdrawal in patients on opioid infusions for 3 to 5 days.²³

A query of the pharmacy dispensing records was used to identify all patients receiving midazolam, fentanyl, and morphine continuous infusions; a manual review of records was performed to assess the duration of infusion for inclusion into the study. Patients were excluded if they were treated with methadone, lorazepam, or a patient-controlled analgesia infusion for ongoing pain and/or anxiety. Also, patients were excluded if the length and outcome of the wean could not be determined owing to reintubation with the resumption of infusions, patient transfer to another facility, or death before completion of the wean. A total of 56 patients (n = 20 [pre], n = 36 [post]) were excluded, based on these criteria.

Before protocol implementation, patients were weaned from opioids and benzodiazepines per attending physician discretion. Withdrawal symptoms were assessed clinically by the bedside nurse without a formalized withdrawal tool and communicated to the physician. Rescue doses of medication and adjustments of the wean in terms of dose, frequency, and weaning interval were made per the attending physician preference.

Demographic data, Pediatric Risk of Mortality (PRISM) scores, and PICU and hospital LOS were obtained from data previously abstracted from PICU patients in the

Virtual PICU Systems, LLC database. Other data were manually abstracted from the patient medical record, including length and total doses of opioids and benzodiazepines received including as-needed doses while on infusions (referred to as "exposure") and as-needed doses during the wean (referred to as "rescue doses"), use of other sedative medications, length of wean, the incidence of adverse events (including the use of naloxone for oversedation and hospital readmission due to withdrawal), and compliance with the protocol. Data were abstracted by 3 of the authors (CER, IS, MV) and interrater reliability was assessed on key variables, with nominal variables requiring complete agreement and continuous variables requiring at least 80% agreement. The overall percent agreement score for key study variables was 99.5%.

Outcomes. Primary Outcome. The primary outcome was the duration of the methadone and benzodiazepine wean. This was calculated from the Medical Administration Record (MAR) by using the time elapsed from the first to the last dose of the weaning medication. For patients discharged home to complete a wean, the length of the wean prescribed was used to calculate the duration in days of the wean.

Secondary Outcomes. Secondary outcomes included total length of hospital stay and time spent in the hospital for purposes of managing the wean. The latter was calculated by review of physician progress notes. If it was stated that the patient was hospitalized for wean management or if there was no other reason noted in the progress note for being hospitalized (e.g., IV medication, oxygen, monitoring), the patient was presumed to be there to complete the wean.

Adverse Events. The use of naloxone during the weaning phase was determined by reviewing the MAR for usage from the first to last dose of weaning medication. The electronic medical record was reviewed to determine if the patient was readmitted within 1 week after discharge. If this occurred, the admission history was used to determine if withdrawal symptoms were noted. The use of rescue medications during the weaning phase was determined from the MAR. Unplanned extubations during the transition from infusions to weaning medications were determined by cross-referencing the patient's medical record number with the unit's unplanned extubation database. These data were not available for the preprotocol cohort because these data were not routinely collected at that time. To evaluate whether the protocol patients experienced either reintubation or delay in extubation due to the weaning medications, progress notes of all postprotocol patients who remained intubated for ≥ 24 hours after initiation of weaning medication, or reintubated, were reviewed to determine the cause.

Protocol Description. Details of the weaning protocol are illustrated in the Figure. The management of patients before the weaning phase was at the physician's

Figure. Opioid and benzodiazepine weaning protocol.

WAT-1, Withdrawal Assessment Tool, version 1.

discretion and no protocols were used to guide therapy in either the preprotocol or postprotocol groups. The duration of opioid and benzodiazepine infusions and most recent infusion dosing were used to generate a weaning plan. Patients were categorized for their risk of withdrawal, based on the length of each of the medi-

cation infusions (opioids and/or benzodiazepines): less than 5 days; 5 up to 13 days; and greater than or equal to 14 days' duration of infusion, which corresponded to a recommended wean schedule of no wean required, short (i.e., daily) wean, and long (i.e., every other day) wean, respectively. These categories were based on

our clinical experience and review of other protocols available before the initiation of our study.^{14,21,22} Starting doses of methadone and lorazepam were calculated from the most recent stable dose of opioid and/or benzodiazepine infusion. To assess the most recent stable dose, the infusion rate the patient received for at least 12 consecutive hours in the previous 24 hours was determined.

To convert opioid infusion dosing to methadone dosing, 50% of the equipotent dose¹⁴ was used to account for methadone's long half-life and high bioavailability. Specifically, the hourly rate of fentanyl (mcg/kg/hr) was multiplied by 0.05 to determine the starting dose of methadone (mg/kg), which was dosed every 6 hours. For morphine infusions, the hourly rate (mg/kg/hr) was multiplied by 1 to determine the starting dose of methadone (mg/kg), which was dosed every 6 hours. Both agents were converted to a maximum dose of 0.2 mg/kg/dose and never more than 10 mg/dose. For midazolam infusions, the hourly rate (mg/kg/hr) was multiplied by 0.5 to determine the starting dose of lorazepam (mg/kg), which was dosed every 6 hours.³ A maximum dose of 0.2 mg/kg/dose and never more than 4 mg/dose was used. As-needed doses, which varied daily, were not included in the determination of the starting doses of medication. If the patient could not tolerate enteral medications, the same dose was given intravenously for both methadone and lorazepam, based on their high oral bioavailability.^{24–26}

Once patients were stable on their weaning medications for 24 hours with Withdrawal Assessment Tool, version 1 (WAT-1) scores < 3, their dose was weaned every day (short wean) or every other day (long wean) by 20% of the starting doses. Withdrawal symptoms were assessed clinically by the bedside nurse using WAT-1.⁶ The WAT-1 was scored every 12 hours and after each rescue dose. If the WAT-1 score was ≥ 3 and the assessment was consistent with withdrawal, "rescue doses" of morphine and/or lorazepam were given. If a patient required >3 rescue doses of morphine and/or lorazepam in 12 hours, the previously scheduled dose on the weaning plan was resumed or, if still on the starting dose, the dose was increased 20%. If patients in the "no wean group" developed withdrawal, rescue doses were given and a short wean could be initiated at the provider's discretion. If excessive sedation was apparent on clinical assessment, dose of medication was held and providers were instructed to proceed to the next step of the weaning plan. The weaning plan, including dosages of weaning medications, duration of the wean, and recommended rescue medication doses, was generated by using an internally developed electronic spreadsheet (Microsoft Excel Microsoft Corp, Redmond, WA). The protocol also included a process to discharge patients on weaning medications if they were considered stable on the wean with no need for rescue doses of medication. This process included joint

family counseling by a pharmacist and nursing on the medication administration and common signs of withdrawal. Additionally, letters detailing the weaning plan and instructions on how to contact hospital physicians for assistance were provided to the families and faxed to their primary care physician.

Protocol Implementation. Before implementation of the protocol, physicians and pharmacists in the PICU and the acute care wards were educated in the conversion from infusions to methadone and lorazepam, and details of the weaning protocol. Nurses, pharmacists, and physicians were trained on the use of the WAT-1 and the protocol's approach to oversedation and withdrawal symptoms. All protocol education was posted on the hospital's evidence-based practice website with easy retrieval using a QR code. By design, audits were not performed during the post protocol implementation phase to avoid artificially enhancing the prescriber's adherence.

Data Analysis. Categorical variables were compared by using the chi-square test or the Fisher exact test. The primary outcome (duration, in days, of methadone and benzodiazepine wean) and additional non-parametric continuous variables were assessed by using the Mann-Whitney *U* test. The Cox proportional hazards regression model was used to assess the effect of protocol implementation and potential confounding variables on the length of hospital stay. Interrater reliability for key study variables was assessed by using percent agreement scores.²⁷ Statistical significance was determined on the basis of an alpha value of less than 0.05. Data analysis was performed with SPSS Statistics version 17.0 (SPSS Inc, Chicago, IL) and Stata Statistical Software version 14.2 (StataCorp, College Station, TX).

Results

Demographics. A total of 177 patients on opioid and/or benzodiazepine infusions for greater than 3 days were included in the study. A total of 75 patients were from the period before protocol implementation ("pre," June 2012–June 2013) and 102 patients were from the period after implementation of a standardized weaning protocol for methadone and lorazepam ("post," March 2014–March 2015). Patient demographics and clinical characteristics are shown in Table 1.

Protocol Compliance. Compliance was assessed retrospectively in the postimplementation group for patients who received a weaning plan. Methadone dosing consistent with the protocol was initiated in 84.4% ($n = 65/77$) of patients. A total of 74% of patients ($n = 57/77$) were weaned from methadone per the protocol, which included recommended steps to take in the event the patient was judged to be oversedated or exhibited withdrawal symptoms as outlined in the Figure. Reasons for deviations from the protocol included provider preference ($n = 12$), reasons unknown on a retrospective review ($n = 5$), delay in extubation requiring additional

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Pre protocol (n = 75)	Post protocol (n = 102)	p value
Age, median (IQR); range, yr	0.6 (0.2, 2.9); 0–21.6	0.4 (0.1, 2.6); 0–20.5	0.32
Weight, median (IQR); range, kg	8.0 (4.1, 13.8); 2.6–70.0	6.4 (4.1, 13.2); 2.3–94.3	0.44
Male, n (%)	36 (48.0)	56 (54.9)	0.36
Race, n (%)			
White	50 (66.7)	77 (75.5)	0.24
Black	11 (14.7)	11 (10.8)	0.49
Other/unknown	14 (18.6)	14 (13.7)	1.00
Ethnicity, n (%)			
Non-Hispanic	50 (66.7)	57 (55.9)	0.15
Hispanic	25 (33.3)	38 (37.3)	0.29
Unknown	0 (0)	7 (6.8)	0.02
Patient type, n (%)			
Trauma	7 (9.3)	8 (7.8)	0.79
Postoperative general	16 (21.3)	24 (23.5)	0.86
Postoperative cardiac	9 (12.0)	17 (16.7)	0.52
Medical	43 (57.4)	53 (52.0)	0.54
PICU LOS, median (IQR), days	11.1 (7.4, 15.8)	11 (7.9, 16.2)	0.76
Mechanical ventilation, median (IQR), days	7.4 (4.7, 11.8)	6.9 (5.1, 10.0)	0.75

sedation (n = 2), and provider unintentional delays on transfer to another unit (n = 1). Lorazepam dosing consistent with the protocol was initiated in 86.0% (n = 55/64) of patients. A total of 80% of patients (n = 51/64) were weaned from lorazepam per the protocol. Reasons for deviations from the protocol included provider preference (n = 6), reasons unknown on a retrospective review (n = 5), and delay in extubation requiring additional sedation (n = 2). Five patients in the postprotocol group were discharged home to complete the wean as compared with 8 in the preprotocol cohort.

Exposure. In terms of days of exposure and total exposure in mg/kg, including infusions and as-needed doses of opioids and/or benzodiazepines before weaning, there was no difference between the preprotocol and postprotocol weaning cohorts except for opioid exposure, which was higher in the preprotocol short wean group than the postprotocol short wean group (52.1 mg/kg vs 36.2 mg/kg, $p = 0.002$) (Table 2). Among patients who were on infusions for less than 5 days (the no wean required group), the number of days of opioid infusions was fewer in the preprotocol group (3.8 vs 4.5 days; $p = 0.025$), while the total exposure to benzodiazepines was higher (10.9 vs 6.0 mg/kg; $p = 0.003$) in the preprotocol group (Table 2).

Exposure to other sedatives while patients were on infusions, before weaning, were similar except for clonidine ($p = 0.019$) and chloral hydrate ($p = 0.005$), which were used more frequently before protocol implementation (Table 3). There was no difference in the

use of clonidine in the weaning phase between groups when withdrawal would have occurred.

Outcomes. Primary Outcome. Patients in the postprotocol group had a significant reduction in the length of the opioid wean, with a reduction in the short wean group from a median of 8.5 days to 5.7 days ($p = 0.001$), and in the long wean group, from 29.7 days to 11.5 days ($p = 0.003$) (Table 4). Similarly, there was a significant reduction in the length of benzodiazepine wean, with a reduction in the short wean group from a median of 8.1 days to 5.2 days ($p = 0.020$), and in the long wean group, from 27.4 days to 9.3 days ($p = 0.011$).

Secondary Outcomes. The LOS in the PICU, PRISM scores, duration of midazolam infusion, and a second admission to the PICU correlated with a longer LOS in a multivariate regression analysis using a Cox proportional hazards model ($p < 0.05$), whereas the weaning protocol did not affect LOS (Hazard Ratio = 1.1; $p = 0.58$; 95% CI, 0.79–1.5). Other potential explanatory variables that were included in the analysis but were not significant confounders were patient age, duration of opioid infusion, total opioid infusion dose, total midazolam infusion dose, and duration of methadone and/or lorazepam wean. There was no difference in the number of patients hospitalized additional days solely for the management of the wean, 4% (n = 3/75) vs 1% (n = 1/102), in the preprotocol and postprotocol implementation groups, respectively.

Adverse Events. There was no difference in complications between the preprotocol and postprotocol

Table 2. Opioid and Benzodiazepine Exposure While on Infusions

Category	Pre-Protocol	Post-Protocol	p value
Opioid infusion, median (IQR), days			
No wean (n = 20, 24)	3.8 (3.5, 4.3)	4.5 (3.8, 4.7)	0.025
Short wean (n = 45, 68)	7.8 (6.5, 10.3)	7.6 (5.9, 9.5)	0.348
Long wean (n = 9, 9)	21.0 (16.8, 33.5)	19.4 (16.1, 24.7)	0.453
Total opioid exposure, mg/kg, median (IQR)*			
No wean (n = 20, 24)	18.0 (11.1, 28.7)	18.7 (12.0, 26.5)	1.00
Short wean (n = 45, 68)	52.1 (37.5, 68.1)	36.2 (24.8, 51.9)	0.002
Long wean (n = 9, 9)	166.2 (133.5, 440.9)	172.1 (93.4, 236.5)	0.436
Benzodiazepine infusion, days, median (IQR)			
No wean (n = 18, 21)	4.3 (3.7, 4.6)	4.2 (3.8, 4.6)	0.821
Short wean (n = 43, 55)	8.0 (6.3, 10.2)	7.7 (6.0, 9.5)	0.376
Long wean (n = 9, 8)	20.9 (16.5, 28.1)	21.3 (15.7, 24.8)	0.885
Total benzodiazepine exposure, median (IQR), mg/kg			
No wean (n = 18, 21)	10.9 (8.8, 14.9)	6.0 (4.6, 10.8)	0.003
Short wean (n = 43, 55)	21.2 (14.5, 40.6)	17.5 (12.3, 27.9)	0.230
Long wean (n = 9, 8)	93.1 (68.1, 172.8)	42.6 (36.9, 51.9)	0.074

* Opioid amount in morphine equivalents.

groups in terms of oversedation requiring the use of naloxone (none in both groups), re-admittance to the hospital for withdrawal (2.7% [n = 2] vs 1% [n = 1], or use of rescue doses of morphine median (IQR) 1 (0,3) vs 1 (0,4) or lorazepam 0 (0,2) vs 0 (0,2) for treatment of withdrawal (Table 3). There were no unplanned extubations in the postprotocol cohort during the period of transition from infusions to enteral weaning medications. There were no reintubations or delays in extubation due to oversedation from weaning medications in the postprotocol group.

Discussion

After the implementation of a methadone and lorazepam weaning protocol in a single center, a significant reduction in the duration of methadone and lorazepam wean days for groups at risk of withdrawal, without an increase in adverse events, was found. The study hypothesis was that the protocol would also lead to a reduction in hospital LOS but this was not observed.

Our study is the largest published study on the efficacy of a methadone and lorazepam weaning protocol and confirms the findings of other studies in that a standardized approach to weaning reduces the time to wean patients off opioids^{11,12,14} and, more recently, benzodiazepines.^{3,28}

The design of this protocol incorporated both dose and length of therapy into the individualized wean plan as both factors have been strongly associated with the risk of withdrawal. This approach is similar to the protocol recently published by researchers at Children's

Hospital Los Angeles.^{12,13}

To facilitate timely initiation of weaning plans during weekends or nights when a PICU pharmacist was not readily available, we used an electronic spreadsheet to generate the weaning plan instead of relying on pharmacy support. The wean plan, which included details on the patient infusion history (most recent stable infusion dosage and duration of exposure), was entered into the electronic medical record and assisted in maintaining the integrity of the plan when the patient's care was assumed by a new practitioner or transferred from the PICU, a challenge that has been described by others.²⁹ Because other factors besides exposure affect the incidence of withdrawal, such as age and cognitive impairment,⁹ it is impossible to have a "one size fits all" approach to weaning dose and duration. A strength of our protocol is that it incorporates prescribed steps to manage both withdrawal and oversedation. These prescribed steps provide rapid interventions by bedside providers and prescribers, which is essential for both patient comfort and safety.

Similar to other groups who have studied the efficacy of opioid and/or benzodiazepine weaning protocols,^{11–14,16,21,22,28} we did not incorporate a protocolized approach to the management of these patients while on infusions. Incorporation of a sedation/analgesia protocol may lead to a further reduction in overall medication use, incidence of withdrawal, and length of the weaning process, although the efficacy of this approach has been mixed.^{30,31}

Our study has several limitations. First, our study is a

Table 3. Adverse Effects and Concomitant Medication Exposure

	Pre-Protocol	Post-Protocol	p value
Patients, n	75	102	
Adverse events			
Naloxone use, n (%)	0	0	1.0
Hospital readmission, n (%)	2 (2.7)	1 (1)	0.39
As-needed doses morphine, median (IQR)			
No wean	0 (0.1, 25)	2 (1, 3)	0.086
Short wean	1 (0, 3)	1 (0.4, 25)	0.548
Long wean	1(0, 3)	1 (0, 4)	0.963
As-needed doses lorazepam, median (IQR)			
No wean	0 (0, 0.75)	0, (0, 2)	0.420
Short wean	0 (0, 1)	0 (0, 1.5)	0.103
Long wean	2 (0, 6)	0.5 (0, 1.25)	0.476
Concurrent medications, n (%)			
Propofol*	1 (1.3)	0 (0)	0.434
Dexmedetomidine*	8 (10.6)	15 (14.7)	0.415
Ketamine*	4 (5.3)	3 (2.9)	0.459
Chloral hydrate*	8 (10.7)	1 (1.0)	0.005
Clonidine*	8 (10.7)	2 (2.0)	0.019
Clonidine†	12 (16.0)	11 (10.8)	0.308

* For more than 72 hours during infusions.

† For more than 72 hours during methadone lorazepam wean.

retrospective study at a single center. Our weaning plan may not be as effective in a different institution with different providers and sedation practices. Despite being the largest study on the efficacy of a weaning protocol, our sample size is still relatively small, particularly in the group of patients on infusions for greater than 13 days (long wean). This may affect the validity of the results. Additionally, although the duration of opioid infusions was similar, the total opioid exposure in mg/kg was higher in the preprotocol group than the postprotocol group. The reasons for this are unclear. Although a change in practice could have caused this effect, the

protocol did not involve changes in the management of patients during the preweaning phase, nor was benzodiazepine usage different in the preweaning and postweaning groups (short and long wean). In terms of the effect of this difference in opioid exposure, it should be noted that of the 2 variables affecting the development of withdrawal, multivariate analysis has shown that duration of use exerts a stronger effect than dose.^{19,32} We cannot rule out however that the difference in opioid dose may have led to an increased incidence of withdrawal symptoms in the preprotocol group and therefore longer wean. Another limitation of this study

Table 4. Wean Length by Medication and Exposure

Category	Pre-Protocol	Post-Protocol	p value
Methadone wean length, median (IQR), days			
No wean (n = 20, 24)	0.8 (0.0, 4.7)	0.0 (0.0, 1.7)	0.165
Short wean (n = 45, 68)	8.5 (5.5, 13.7)	5.7 (4.3, 8.0)	0.001
Long wean (n = 9, 9)	29.7 (16.3, 34.8)	11.5 (7.9, 16.2)	0.003
Lorazepam wean length, median (IQR), days*			
No wean (n = 18, 21)	0.2 (0.0, 3.5)	0.0 (0.0, 0.0)	0.183
Short wean (n = 43, 55)	8.1 (4.2, 11.9)	5.2 (3.8, 6.7)	0.020
Long wean (n = 9, 8)	27.4 (15.7, 32.4)	9.3 (6.9, 13.9)	0.011

* Four patients in the lorazepam group received diazepam for their wean.

is that in the preprotocol period our PICU did not have a formal withdrawal assessment tool, and recognition of withdrawal was dependent on the provider's clinical assessment. We are therefore not able to compare rates of withdrawal. Likewise, it is difficult to compare the use of rescue medications for withdrawal between the preprotocol and postprotocol groups because there was no formalized approach to the treatment of withdrawal symptoms before the protocol was implemented, and thus patients experiencing withdrawal may have gone undiagnosed and untreated.

The effect of a standardized wean on overall hospital LOS has been variable in the literature, with some studies noting a decrease^{11,13} and others^{12,24} finding no effect. In our multivariate analysis, LOS was most strongly associated with the degree of illness with variables such as longer PICU stay, a second admission to the PICU, and higher PRISM scores. None of the variables associated with opioid or benzodiazepine exposure while on infusions or weaning were associated with LOS besides the duration of midazolam infusion. This suggests that illness severity is a stronger determinant of LOS and, thus, the effect of the protocol, if any, is too weak to be apparent in a study of this size. We hypothesized that implementation of the protocol with standardized weans and discharge process would reduce the time a patient spends in the hospital for the sole purpose of weaning; however, we did not find an impact, because only a small number of patients remained in the hospital for the sole purpose of completing the wean.

Conclusions

Implementation of an exposure-based opioid and benzodiazepine weaning protocol led to a significant reduction in the duration of time to wean off medication without an increase in adverse events. Further evaluation of this protocol in other pediatric centers is necessary to assess the generalizability of these results.

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Ethical Approval and Informed Consent. Given the nature of this study, the institutional review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Exempted criterion.

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