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OPIOID WITHDRAWAL SIGNS AND SYMPTOMS IN THE PEDIATRIC PATIENT
DURING OPIOID TAPERING

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL IN THE PEDIATRIC PATIENT DURING OPIOID TAPERING

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2012

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Opioids are used routinely in the pediatric intensive care population for analgesia, sedation, blunting of physiologic responses to stress, and safety. In children, physical dependence may occur in as little as two to three days of continuous opioid therapy. Once the child no longer needs the opioid, the medications are reduced over time. A review of the literature revealed that the majority of the published studies used either a neonatal opioid assessment tool or no assessment tool. A subsequent international survey of pediatric providers found a wide range of opioid tapering practices and sporadic use of opioid withdrawal instruments to guide practice. Since tapering routines vary among practitioners, it is not uncommon to see signs and

symptoms of opioid withdrawal. A prospective, descriptive study was conducted to describe the frequency of opioid withdrawal signs and symptoms and to identify factors associated with these opioid withdrawal signs and symptoms. The sample of 25 was drawn from all patients, ages 2 weeks to 21 years admitted to the Children's Hospital of Richmond Pediatric Intensive Care Unit (PICU) and who have received continuous infusion or scheduled opioids for at least 5 days. Data collected included: opioid withdrawal score (WAT-1), opioid taper rate (total dose of opioid per day in morphine equivalents per kilogram [MEK]), pretaper peak MEK, pretaper cumulative MEK, number of days of opioid exposure prior to taper, and age. Out of 26 enrolled participants, only 9 (45%) had opioid withdrawal on any given day. In addition, there was limited variability in WAT-1 scores. The most common symptoms notes were diarrhea, vomit, sweat, and fever. For optimal opioid withdrawal assessments, clinicians should use a validated instrument such as the WAT-1 to measure for signs and symptoms of opioid withdrawal. Further research is indicated to examine risk factors for opioid withdrawal in children.

Key Words: opioid withdrawal, opioid taper, opioid analgesia, critical care, child

CHAPTER 1. INTRODUCTION

Background and Significance

Opioids are used routinely in the pediatric intensive care population for analgesia, sedation, blunting of physiologic responses to stress, and safety.¹⁻³ The therapeutic goal of providing adequate analgesia and sedation often results in days to weeks of continuous exposure to opioids and sedative. Continued exposure may lead to iatrogenic opioid dependence. Opioid dependence is defined as a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.⁴ Opioid withdrawal is a clinical response to the cessation of an opioid after continuous, prolonged exposure to that opioid.⁵ Therefore, it is clinically and ethically prudent to taper opioids in a safe manner with a goal of avoidance of opioid withdrawal.

Presently, there is no gold standard for opioid tapering in children. A review of the literature of the empiric evidence to guide opioid tapering while avoiding opioid withdrawal in children is presented in Chapter 2.⁶

The majority of published research has focused on the periodic incidence of withdrawal symptoms during opioid tapering. Only recently has a valid and reliable pediatric opioid withdrawal symptom assessment instrument- the Withdrawal

Assessment Tool (WAT-1)⁷ been developed and this tool is reviewed in Chapter 2. In addition, only one study conducted in an adult and pediatric population analyzed the effect of use of an opioid taper algorithm on occurrence and nature of opioid withdrawal symptoms. Once clinicians can recognize risk factors for opioid withdrawal and can appropriately assess their patients using a validated opioid withdrawal instrument, the goal of tapering an opioid properly while avoiding opioid withdrawal is possible.

Although the WAT-1 was published in 2008⁷, except for the initial and subsequent validation studies for the WAT-1, no studies have been conducted using a validated pediatric opioid withdrawal assessment tool to describe the frequency of opioid withdrawal as well as factors that affect the frequency. Since little information is known about opioid withdrawal in a pediatric population, a study describing the frequency of opioid withdrawal signs and symptoms and to identify factors associated with opioid withdrawal is presented in Chapter 3.

A prospective, longitudinal descriptive study was initiated to explore the frequency of opioid withdrawal and detect associated risk factors in a pediatric population. The specific aims of this study were to: (1) describe the signs and symptoms of opioid withdrawal in children undergoing opioid tapering; and (2) examine the relationship among opioid withdrawal signs and symptoms, opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate and the child's age. Permission for inclusion in the study was obtained from parents or legal guardians. Twenty six participants were enrolled. Demographic data was collected to describe the sample. To identify opioid withdrawal signs and symptoms, the WAT-1⁷ was used daily. Opioid exposure prior to study enrollment was calculated and all opioids

converted to morphine equivalents. Each day's previous twenty-four hours opioid exposure was calculated and converted to morphine equivalents per kilogram (MEK). All participants were assessed for opioid withdrawal daily for up to 7 days. Participant characteristics were examined for possible association with opioid withdrawal.

On any given day, opioid withdrawal was noted in half (n=12) of the participants. The most common signs of opioid withdrawal were diarrhea, vomiting, sweating and fever. Of those participants who had opioid withdrawal, the level of severity, based on WAT-1 scores, was not severe. In addition, for those patients with opioid withdrawal, the effect of previously reported risk factors was examined. There was no relationship between peak opioid dose and opioid withdrawal. We found a relationship between opioid duration and withdrawal that approached significance ($r=0.36$; $p\text{-value}>0.07$), showing that as opioid duration increased, opioid withdrawal increased. In addition, as cumulative opioid dose increased, withdrawal increased ($r=0.33$; $p>0.09$).

This study contributes new knowledge to the description of signs and symptoms of opioid withdrawal in the pediatric patient undergoing opioid tapering. We believe this is the first study to be conducted using the WAT-1 to measure signs and symptoms of opioid withdrawal in children. The investigators who developed and validated the WAT-1 found that opioid duration and cumulative dose were predictors of risk of opioid withdrawal. In conjunction with the evidence reported by the investigators who developed and validated the WAT-1 scale, this evidence should inform clinicians of the potential risk factors as well as signs and symptoms of opioid withdrawal in children. Improvements in opioid management may lead to higher patient satisfaction, decreased length of stay and decreased suffering.

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CHAPTER 2. OPIOID TAPERING IN CHILDREN: A REVIEW OF THE LITERATURE

Background

Routine sedation and analgesia for ventilated children in the intensive care unit is standard practice. Unfortunately, the therapeutic goal of providing adequate analgesia and sedation often results in days to weeks of continuous exposure to opioids and sedatives. Continuous exposure results in iatrogenic opioid and sedative dependence. In children, physical dependence has been found to occur in as little as two to three days of continuous opioid therapy.¹ Tolerance to opioids has been seen to develop even more rapidly in neonates and infants.² Once the child no longer needs the opioid or sedatives, the medications are weaned. Since tapering routines vary among practitioners, it is not uncommon for nurses to witness symptoms of opioid withdrawal in this vulnerable population. Opioid withdrawal symptoms include hiccups, goose bumps, chills, fever, tachycardia, tachypnea, hypertension, agitation, restlessness, insomnia, nausea, vomiting, diarrhea, cramps, lacrimation, rhinorrhea, yawning, diaphoresis, mydriasis, bone pain, muscle aches and spasms, and seizures.¹ Acute effects of withdrawal symptoms are numerous. Diarrhea and vomiting can lead to dehydration. Tachycardia may lead to unnecessary IV fluid boluses or even cardiology evaluations. Routine use of validated opioid withdrawal assessment tools or algorithms is rare, which

contributes to delays in diagnosis of opioid withdrawal syndrome and proper treatment. Potential long term effects of poorly managed withdrawal symptoms are unknown; however, possible consequences include prolonged tapering duration in response to attempts to alleviate withdrawal symptoms as well as needless physical and emotional suffering. Of note, only one position statement on drug withdrawal was discovered during the search. The American Academy of Pediatrics (AAP) has a position statement on neonatal drug withdrawal with recommendations that include multimodal maternal screening for opioid use, enhanced recognition of signs of opioid withdrawal, routine use of appropriate opioid withdrawal tools, and medication recommendations for opioid or sedative withdrawal.³ However, no such statement exists for the pediatric population. The purpose of this critical review of the literature was to synthesize and critically analyze published research and other critical reviews on opioid withdrawal management in children.

METHODS

A search of the major databases for English language publications included Cochrane, MEDLINE, CINAHL and PsychInfo. Keywords used included: “opioid”, “withdrawal”, “abstinence”, “infant” and “child” (n=114). The resulting group was then limited to 1980-2009 (n=93). Age limits were set at one month to eighteen years of age. Even though there is a wealth of information regarding opioid abstinence syndrome in neonates, studies pertaining to premature neonates or infants born to mothers on opioids were excluded due to the neurodevelopmental differences in manifestations of opioid abstinence syndrome. Two articles were excluded since they were inaccessible. The remaining articles were reviewed for relevance to the purpose of the review (n=20).

Articles were included if the focus remained on a pediatric population undergoing opioid tapering. Due to the relatively small sample size, articles that included a mix of pediatric patients and adult patients were included. Opinions, editorials and individual case studies were not included. In addition, articles that studied the efficacy of a prophylactic pharmaceutical intervention were excluded. The remaining articles were assessed for inclusion criteria. Thirteen papers met the criteria for review.

DATA COLLECTION AND ANALYSIS

Once accepted for review, the main aspects of each article were extracted and summarized in table format. These thirteen papers were categorized into five groups determined by the main focus of the research: opioid tolerance in children (n=1); incidence of opioid withdrawal (n=6); review articles (n=2); use of algorithm or protocol (n=1); validation of assessment tools in pediatric population (n=3). The table was further delineated into five columns: year, authors, sample, design and key findings. (See Table 1) Conclusions from each of the articles were reviewed and examined for emerging themes. Upon completion of tabulation, findings were reviewed and assessed for correlations and similarities.

RESULTS

Opioid tolerance in children. Only one study was found that reviewed opioid tolerance in children and infants.⁴ Scales reviewed were all validated in neonatal populations. The authors concluded that opioid withdrawal could be avoided with the use of appropriate tapering protocols and assessment tools. Should signs of withdrawal occur, pharmacological and non-pharmacological interventions were suggested. Non-pharmacological intervention suggestions included rocking, swaddling, reduced

environmental stimulation and frequent feedings. Pharmacological recommendations for length of taper correlated with length of exposure to opioids. Specifically, if opioid exposure was less than one week, tapering could occur over three days. For infants exposed to over one week of opioids, a less aggressive protocol, tapering over two to three weeks, was recommended.

Opioid withdrawal symptoms in children. Six studies examined the incidence of opioid withdrawal symptoms in children undergoing opioid taper. All but one of the studies was conducted in a pediatric intensive care unit (PICU). Katz, Kelly and His examined the occurrence of opioid withdrawal in critically ill children who had received continuous infusion fentanyl for greater than twenty-four hours.⁵ Using the Neonatal Abstinence Scoring Scale (NAS) on a population (n=23) of children ranging in age from one week to twenty-two months, they found a high incidence of opioid withdrawal that was both dose and duration dependent. It should be noted that the practitioners used a very aggressive weaning regimen entailing a dose reduction of fifty percent each day for two days and then discontinuation of the opioid on day three. Subsequent research has found that this type of rapid taper, which was the norm at the time, invariably results in withdrawal. A few years later, Carnevale and Ducharme conducted an observational study to examine adverse reactions to opioid and benzodiazepine withdrawal in critically ill children.⁶ Although their study was limited by the small sample size (n=5) and the lack of a validated assessment tool, the resulting observations of relationships between types of behavioral symptoms across a variety of clinical contexts did contribute to the generalizability of opioid withdrawal symptoms over multiple patient populations. In 2005, the same authors used a prospective multiple case study design to observe the

effects of variable weaning rates on incidence of opioid and benzodiazepine withdrawal symptoms.⁷ The pediatric intensive care unit patients (n=27) ranged in age from one month to nineteen years. Again, the authors used a relatively small sample size and did not use a validated assessment tool and instead relied on data collection gleaned from nurses' notes. Despite these limitations, the authors did note the need to tailor the percentage of wean to the length of time on opioids. Pederson and Parran used a daily patient self-report log on a post hematopoietic cell transplant cohort of patients ranging in age from seven to sixty-four years and found that the length of taper needed to avoid withdrawal symptoms correlated with both pretaper opioid dosage and length of pretaper opioid therapy.⁸ Furthermore, withdrawal symptoms were highest on taper days two through six. In a prospective repeated measures design study using the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC), Ista and colleagues found that the most common symptoms of opioid withdrawal in children ranging in age from zero days to sixteen years (n=79) included sleeplessness, increased temperature, diarrhea, tremors and pupil dilation.⁹ Only one randomized double blinded trial was found.¹⁰ PICU patients (n= 37) with an average age of nine years were randomized to a five or ten day weaning protocol with both groups receiving enteral methadone. The authors found no significant difference between the five day and ten day wean groups. Limitations of this study include the small sample size and the use of an assessment tool (NAS) only validated for assessment of neonatal abstinence.

Opioid withdrawal review articles. Due to the paucity of articles related to pediatric opioid withdrawal, two review articles were included. Ista and colleagues

published a literature review with similar recommendations to employ strategies to decrease the amount of opioid administered.¹¹ Since the majority of studies conducted on children used assessment tools validated in a neonatal population they may have produced unreliable results. The authors conclude that an appropriate assessment tool for use in the pediatric population is sorely needed. During the same year, Bartolome and colleagues published a literature review with the intent of gleaning analgesia and sedation management recommendations from the existing body of evidence.¹² As with the Ista group, the authors found many gaps in the existing literature including the existence of an appropriate assessment tool to facilitate avoidance of adverse effects such as opioid withdrawal.

Opioid withdrawal assessment tools for children. Only two studies attempted to develop an opioid withdrawal tool for children.^{13, 14} Both tools were developed by the same team of researchers. In fact, the latter tool is merely a revision of the first tool. The Opioid Benzodiazepine Withdrawal Scale (OBWS), a 21 item assessment instrument, was tested in PICU patients who were undergoing opioid and benzodiazepine tapering. Out of fifteen patients, thirteen experienced symptoms of withdrawal despite the use of a tapering protocol and the OBWS. The most common symptoms witnessed were sleeplessness, tremors, mydriasis and diarrhea and occurred as late as six days after a greater than ten percent taper in opioid. Initial psychometrics were adequate, but could be improved (sensitivity= 0.50; specificity=0.87). A subsequent multicenter prospective repeated measures study assessing the predictive validity of a newly revised nineteen item scale ensued. The resulting Withdrawal Assessment Tool-1 (WAT-1) effectively

replaces the first tool with its far superior psychometric performance (sensitivity= 0.872; specificity=0.88).¹⁴

One study developed an opioid and benzodiazepine withdrawal scale for children. The Sophia Observation Withdrawal Symptoms scale (SOS) is a 15 item scale that takes into account the overlap of opioid and benzodiazepine symptoms of withdrawal.¹⁵ In comparison to the WAT-1 (7 minutes), the SOS takes a mere 2 minutes to complete.

Algorithms or protocols for opioid weaning. Within all of the included articles, the authors allude to varying opioid tapering practices (Table 2). Only one study used an assessment based tapering algorithm. Parran and Pederson conducted a quasi-experimental study that tested the impact of use of an opioid tapering algorithm on the incidence of opioid withdrawal symptoms.¹⁶ Their study included 106 patients who were one month post hematopoietic cell transplant. The ages of participants ranged from 5 to 64 years. The authors concluded that the total reports of withdrawal symptoms positively correlated with length of taper ($r=0.46$, $p<0.001$). That is, with a longer taper, there were fewer symptoms of withdrawal. Overall, the results indicated a decrease in incidence of opioid withdrawal symptoms for those patients who were tapered with use of the opioid taper algorithm.

Conclusions

Implications for Practice. This review supports the need for a pediatric opioid withdrawal assessment tool with excellent psychometric properties that can be used in a variety of settings. The WAT-1 instrument certainly appears promising. Since the majority of PICUs routinely use a combination of benzodiazepines and opioids for

sedation and analgesia, the recently published development of the SOS scale, with its short application time and attention to both opioid and benzodiazepine withdrawal symptoms, merits a deserved second glance. Several studies demonstrated the need for adherence to a dose and duration dependent tapering protocol with ongoing assessment and reassessment for withdrawal symptoms.

Multiple opportunities abound for the advanced practice nurse to positively influence practice and outcomes. In order to avoid immediate and potentially long term harm, the advanced practice nurse can lead the development of evidence based practice guidelines for opioid tapering in the pediatric population. By using the information drawn from a validated opioid withdrawal assessment tool to guide practice, the advanced practice nurse has the ability to individualize the opioid tapering plan for each child. Besides the obvious ethical implications of prevention and treatment of suffering, the advanced practice nurse has the ability to contribute to the overall care of the patient by providing optimal symptom management and efficient, assessment based opioid tapering. As we enter into an era of ever increasing restrictions on the provision of and reimbursement for health care, the advanced practice nurse is in an ideal position to guide care with a goal of prevention of unnecessarily lengthy hospitalizations. Overall, the efficacy of an assessment-based opioid tapering regimen may result in improved patient outcomes, greater provider satisfaction and confidence, enhanced family satisfaction and potential cost savings.

Implications for Research. With the advent of validated, pediatric-specific, opioid withdrawal instruments, opportunities abound for future research. Further research is needed to test the WAT-1 and SOS tools in settings outside of the PICU. Replicative

studies are now possible substituting an appropriate assessment instrument for the pediatric population such as the WAT-1 or the SOS for the NAS. Although the focus of the majority of the studies was the incidence of withdrawal symptoms experienced by the children, the tapering protocol used for and during the studies provides guidance for the future development of an evidence-based tapering algorithm. Additional studies of importance include evaluation of improved outcomes such as decreased length of stay, decreased length of taper, and avoidance of unnecessary diagnostic testing secondary to enhanced capability to accurately assess and diagnose withdrawal.

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Table 1. Studies Included in Critical Review				
Year	Authors	Sample (age)	Design	Key Findings
1994	Anand & Arnold	NA	Literature Review	NAS preferred
1994	Katz, Kelly & His	23 (1 wk-22m)	Prospective, case series	↑ withdrawal seen in >5 days duration of therapy
1997	Carnevale & Ducharme	5 (2m-16m)	Prospective, multiple case study	inconsolable crying, tremors, jitteriness, irritability, gagging, vomiting & feeding problems < 24 hr post wean
2000	Pederson & Parran	45 (7-64 yrs)	Prospective, descriptive	Withdrawal symptoms highest on taper days 2 through 6 Length of taper correlated with both pretaper opioid dosage & length of pretaper opioid therapy.
2002	Parran & Pederson	106 (5-64 yrs)	Quasi-experimental	Positive relationship between length of taper & total reports of withdrawal symptoms (r= 0.46, p<0.001)
2004	Franck et al.	15 (6wks – 28m)	Prospective, repeated measures	OBWS developed Sensitivity = 0.50 Specificity = 0.87
2005	Berens, et al.	37 (36 wks – 18yr)	Prospective, randomized double blind methadone wean	No difference in withdrawal between 5 day or 10 day methadone wean
2005	Ducharme et al.	27 (1m- 19 yr)	Prospective, multiple case study	Final weaning recommendations: 1-3 day= 20% wean per day 4-5d= <20% wean per day 6-7d= 13% wean per day 8-14d= 8-13% wean per day 15-21d= <8% wean per day >21d= 3% wean per day
2007	Bertolome, Cid & Freddi	NA	Literature review	Lack of individualized tapering regimens
2007	Ista et al.	NA	Literature review	Overlap of withdrawal symptoms for opioids & benzodiazepines
2008	Franck et al.	83	Multi-centered prospective psychometric evaluation	OBWS revised to create WAT-1 WAT-1 validated Sensitivity = 0.87 Specificity = 0.88
2008	Ista et al.	79 (0-16 yrs)	Prospective, repeated measures	Most frequent symptoms= Sleeplessness, ↑temp, diarrhea, tremors & pupil dilation
2009	Ista et al.	79 (0-16 yrs)	Instrument validation	SOS developed

d=day; m= month; NA= non-applicable; NAS= Neonatal Abstinence Score; OBWS= Opioid Benzodiazepine Withdrawal Scale; SOS= Sophia Observation withdrawal Symptoms scale; wk=week; WAT-1= Withdrawal Assessment Tool; ↑= increased

Table 2. Summary Tapering Techniques During Opioid Weaning

Year	Authors	N	Age	Opioid (O) or Benzo (B)	Assessment Tool	Tapering Technique	Incidence of Withdrawal Symptoms
1994	Katz, Kelly & His	23	< 2 years	Fentanyl	NAS	Fentanyl weaned 50% every 24h	57%
1997	Carnevale & Ducharme	5	2m - 16m	O & B	No tool sited	>25% to 50% within 24 hours	100%
2002	Parran & Pederson	106	5-64 years	O	0-10 or FACES 14 symptom withdrawal log Interview Medication Profile	Algorithm	16%
2004	Franck et al.	15	6wk – 28m	O & B	OBWS Nurses' clinical judgement Medical record review	>14 days = 10% daily ↓ > 5 days = 20% daily ↓	87%
2005	Ducharme	27	0 – 19 yrs	O & / or B	Nurses' notes	Duration of exposure (recommended daily wean) a) 1-3 days (20%) b) 4-7 days (13-20%) c) 8-14 days (8-13%) d) 15-21 days (<8%) e) > 21 days (3%)	NA
2008	Ista et al.	79	0-16 yrs	O & B	SBOWC	↓ morphine by 10 µg/kg/hr every 24h; ↓ midazolam 50µg/kg/hr per 8 hrs	34%

Benzo = benzodiazepine; hr = hour; hrs= hours; kg= kilogram; µg = microgram; m= month; N= sample size; OBWS = Opioid Benzodiazepine Withdrawal Scale; SBOWC= Sophia Benzodiazepine and Opioid Withdrawal Checklist; NAS= Neonatal Abstinence Scoring System ; wk= week; yrs=years; ↓= decrease

CHAPTER 3. OPIOID WITHDRAWAL SIGNS AND SYMPTOMS IN CHILDREN: FREQUENCY AND DETERMINANTS

INTRODUCTION

Over 90% of critically ill children receive opioids.² Routine use of analgesia and sedation for critically ill, ventilated children is essential for the child's comfort and safety and to protect the child from self-harm due to unplanned endotracheal extubation, anxiety related increased oxygen demand and ventilator dyssynchrony.⁸ However the therapeutic goal of providing adequate analgesia and sedation often results in days to weeks of continuous exposure to opioids and sedatives. Continuous exposure may result in iatrogenic opioid and sedative dependence. Opioid dependence is defined as a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.⁴ Opioid tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.⁴ Once the child no longer needs the opioid or sedative, the medications are reduced over time. The goal of tapering is to safely wean the opioid dose while avoiding opioid withdrawal. Opioid withdrawal refers to signs and symptoms that occur following an abrupt discontinuation or rapid decrease in an opioid after opioid dependence has developed. Unfortunately, there is little empirical evidence to guide the practice of opioid tapering.^{3,9,10} Since opioid tapering practices vary among practitioners, it is not uncommon for nurses to witness signs and symptoms of withdrawal in this vulnerable population. Opioid withdrawal signs and symptoms in

children include diarrhea, nausea, vomiting, fever, sweating, mottling, tremor, agitation, frequent yawning, frequent sneezing, motor disturbance, insomnia and hypertonia.^{1,3,7,9-}

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Few data have been published on the incidence of opioid withdrawal in the pediatric population with the reported incidence of opioid withdrawal varying widely (0-100%).^{1,9,11,20} In addition, studies of opioid withdrawal conducted in the pediatric population have used neonatal withdrawal tools^{1,9,11,20-22} or no opioid assessment tool.⁹⁻¹² The use of developmentally inappropriate tools such as neonatal opioid withdrawal tools may result in conclusions that are flawed. In 2008, Franck et al. developed the Withdrawal Assessment Tool-1 (WAT-1) (Fig 1), a pediatric opioid withdrawal scale.^{3,10} Presently, the WAT-1 is the only validated pediatric opioid withdrawal assessment tool. Although another tool, the Sophia Observation withdrawal Symptoms scale (SOS), has also been developed, its psychometric properties have yet to be published.¹³ Except for the initial and subsequent tool validation studies of the WAT-1, no studies have been conducted to identify the incidence of pediatric opioid withdrawal using a validated pediatric opioid withdrawal assessment tool.^{7,23} In addition there are few data about factors that may affect the frequency of withdrawal signs and symptoms including opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate, and the child's age.^{1,3,7,9-14,16-21,24} Further, PICU length of stay (LOS)⁷, duration of mechanical ventilation (LOMV) and cumulative opioid dosage (mg/kg) are positively associated with signs and symptoms of opioid withdrawal.^{7,19,20} Although associations among opioid duration^{9,17,20,21} and cumulative dose^{20,21} prior to taper and occurrence of opioid withdrawal signs and symptoms have been identified, data

concerning other factors (peak opioid dose⁹, opioid taper rate and age⁷) that may affect opioid withdrawal signs and symptoms are limited.

Although pediatric guidelines for opioid tapering exist, they are based on little empiric evidence.^{1,9,25,18,25} In order to describe present opioid tapering practices by pediatric practitioners, we conducted a cross-sectional web based survey¹⁴ using international pediatric pain and palliative care email list serves. Of the 104 respondents, only 22 (27%) had a written protocol for opioid tapering. Respondents without a protocol reported regimens for opioid withdrawal that varied greatly. In addition, only half of the respondents (n=52) used an opioid withdrawal assessment tool. Of those using an assessment tool, the majority used the WAT-1 (n=22) followed by the Finnegan Neonatal Abstinence Score (NAS) (n=14).¹⁴

This study will investigate the incidence of opioid withdrawal and factors associated with development of opioid withdrawal in a pediatric population. More importantly, our study will measure opioid withdrawal using a validated, pediatric tool – the WAT-1. Accurate assessment of opioid withdrawal is important for several reasons. The acute effects of withdrawal not only result in discomfort but can be dangerous as well. Diarrhea and vomiting can lead to dehydration and tachycardia may lead to unnecessary intravenous fluid resuscitation or cardiology evaluations. Poorly managed signs and symptoms of opioid withdrawal may lead to prolonged LOS. Therefore, the purpose of this study is to describe the frequency of opioid withdrawal signs and symptoms and to identify factors associated with these opioid withdrawal signs and symptoms. The specific aims of this study are to (1) describe the signs and symptoms (WAT-1) of opioid withdrawal in children undergoing opioid tapering and (2)

examine the relationship among opioid withdrawal signs and symptoms (WAT-1), opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate, and the child's age.

METHODS

Setting and Sample

The study was conducted in the Pediatric Intensive Care Unit (PICU), the Pediatric Progressive Care Unit (PPCU) and the acute care pediatric units at the Children's Hospital of Richmond, Virginia Commonwealth University Health Systems (VCUHS). The PICU, the PPCU and acute care areas, admit children with a wide range of pediatric diagnoses enhancing generalizability of study findings.

The sample of 26 were drawn from all patients, ages 2 weeks to 21 years, admitted to the PICU who had received continuous or scheduled infusion opioids for greater than 5 days.^{1,7,17,20} Previous studies have found that opioid tolerance may occur after 5 days of opioid exposure^{18,20,26} and that opioid withdrawal signs and symptoms are highest during taper days 1 through 6. Therefore children were enrolled in the study and data collection occurred daily up to 7 days.^{3,11,12,21,27} Pediatric patients (2 weeks to 21 years) from all ethnic and racial backgrounds were recruited. Since restlessness is part of the WAT-1 evaluation, children with paralysis of one or more limbs or who were receiving neuromuscular relaxants were excluded.

Measurement of Key Variables

Opioid Withdrawal Signs and Symptoms. Opioid withdrawal signs and symptoms were measured using the 11 item Withdrawal Assessment Tool – 1(WAT-1) (Fig 1). The WAT-1 is a pediatric opioid withdrawal tool that evaluates three categories of symptoms

with symptom scores ranging from either 0-1 or 0-2 based on the type of symptom and its severity. It includes measures of gastrointestinal symptoms (diarrhea, nausea, vomiting), autonomic (fever, sweating) and central nervous system (tremor, sedation state, uncoordinated movement, yawning or sneezing, startle to touch, muscle tone and time to gain calm) signs and symptoms of opioid withdrawal.⁷ The 19 item WAT-1 was tested in a pediatric critical care population (n=83; 1040 observations) ranging in age from 6 months to 10 years. Redundant signs and symptoms and symptoms with low levels of association with withdrawal intensity ratings were eliminated resulting in the current recommended 11 item (12 point) tool. The original validity and reliability testing revealed high sensitivity (0.87) and specificity (0.88). Further psychometric evaluation of the tool was conducted in a multicenter prospective repeated measures design study which included pediatric critical care and general care patients (n=126; 836 observations).²³ The WAT-1 has four steps. First, the previous 12 hours are reviewed for stooling, vomiting and fever. Second, the subject is observed for 2 minutes prior to any stimulus for behavior state, tremor, sweating, uncoordinated movement, yawning and sneezing. Third, a 1-minute progressive stimulus is used to assess startle to touch and muscle tone and fourth, a post stimulus observation is used to assess time to gain calm. Total WAT-1 scores range from 0-12 and a score of 3 or greater indicates presence of opioid withdrawal.⁷

Opioid Exposure. Withdrawal signs and symptoms may be affected by both the opioid cumulative and peak dose administered during opioid therapy. Therefore opioid exposure will include these variables as well as opioid duration. Previous studies have shown that the duration of opioid receptor occupancy is related to the development of

opioid tolerance.^{3,22,28,29} In a prospective study conducted by Katz et al. (1994), 23 infants (<23 months) were observed for signs of opioid withdrawal post opioid exposure using the Neonatal Abstinence Scale, an tool designed for the neonatal population.²⁰ They found a positive correlation of dosage ($p<0.005$) and length of exposure ($p<0.0001$) with opioid withdrawal symptoms. In fact, a cumulative dose of 2.5mg/kg fentanyl or more than 9 days exposure was 100% predictive of withdrawal. Although the results of these studies are compelling, study limitations, including small sample size, narrow age range and use of a developmentally inappropriate tool may affect generalization to the pediatric population. Further, the relationship between peak opioid dose and opioid withdrawal is limited to one study.⁹ In a prospective study of critically ill children (n=27), Ducharme et al.⁹ found a significant relationship ($r=0.34$; $p<0.05$) between peak opioid dose and opioid withdrawal. However, opioid withdrawal was measured indirectly by reviewing nurses' documentation.

Opioid Dose. Several previous studies have found a relationship between cumulative opioid dose and opioid withdrawal although most have been either conducted in infants only or in pediatrics using a measurement tool designed for infants. In one of the first studies to investigate the relationship between potential risk factors (opioid exposure and withdrawal) using a prospective study of infants ranging in age from 1 week to 22 months, Katz et al. found that a total dose of 1.5mg/kg was associated with a 50% rate of opioid withdrawal.²⁰ Other studies conducted in children have found a similar dose dependent relationship.^{9,21,26} In a prospective, multiple case study (n=27), Ducharme and colleagues examined the effects of variable opioid taper rates on occurrence of opioid withdrawal on PICU patients (age 0-19 years). They found

a small but significant association between opioid peak dose and occurrence of withdrawal ($r=0.34$; $p<0.05$).⁹ One opioid specific study examined the relationship between fentanyl, the preferred opioid in pediatric critical care, and opioid withdrawal. In this prospective, descriptive opioid withdrawal study of critically ill infants and young children (< 25 months), French and Nocera found a strong correlation between cumulative fentanyl dose and opioid withdrawal score ($r=0.76$; $p<0.01$).²¹ Likewise, in a retrospective study of neonates, Arnold and colleagues found a total dose of 1.6mg/kg to be associated with the development of opioid withdrawal.²⁶ However all of the results described here are limited by narrow age range of the study populations, small sample sizes and the use of opioid withdrawal assessment tools designed for neonates in an older population. Because the literature shows a relationship between cumulative and peak opioid dose on occurrence of opioid withdrawal, opioid dose was described as both cumulative and peak.^{9,20,21,26}

To compare analgesics across types, all opioids were converted to morphine and reported as morphine equivalents per kilogram (MEK).^{12,17} For this study, fentanyl conversion to morphine was calculated by the formula 10mg of IV morphine = 0.1mg IV fentanyl.³⁰ Daily dose of MEK was calculated. Peak and cumulative MEK were calculated pretaper and daily during taper. The largest daily MEK was recorded as the peak opioid dose. Cumulative dose was determined by summation of daily MEKs prior to initiation of opioid taper.

Opioid Duration. Previous studies have found that duration of opioid exposure effects opioid withdrawal. Ducharme and colleagues found a moderate association between opioid duration and occurrence of opioid withdrawal ($r=0.41$; $p<0.01$).⁹ Katz et

al. found that a duration of 5 days or more of fentanyl exposure was 50% predictive of opioid withdrawal.²⁰ French and Nocera found a significant correlation between duration of fentanyl exposure and opioid withdrawal score ($r=0.70$; $p<0.05$).²¹ In a prospective, repeated measures design study of critically ill children ($n=79$; ages 0 to 16 years), Ista and colleagues found a significant correlation between duration of opioid exposure and severity of opioid withdrawal ($r=0.52$; $p<0.001$).¹⁷ In this study opioid duration was calculated as the number of days of continuous or scheduled opioid exposure prior to initiating opioid taper. Only children with at least 5 days of opioid exposure were eligible for the study.

Opioid Taper Rate. Although opioid tapering recommendations exist in the literature, few are based on empiric evidence.^{1,9,18,25,31} Since rates of taper vary depending on clinician, opioid tapering rate was defined as dose change per day, expressed in morphine equivalent units per kilogram (MEK) of the child's body weight. Nonscheduled opioids that were administered were included in the daily opioid tapering rate calculation. The MEK/day was compared to the previous day's MEK/day dose. In addition, medications that may alleviate withdrawal signs and symptoms such as benzodiazepines, α -adrenergic (clonidine, dexmedetomidine), antiemetics and antipyretics were recorded.

Procedures

Prior to beginning the study, an informational in-service was provided to the pediatric nursing leadership and staff of the involved units. The study was approved by the VCU Institutional Review Board at VCU and included waiver of assent since the pediatric participants were sedated during the observation period. Permission was

obtained from the parent/legal guardian at time of study enrollment. Patients who met selection criteria were identified through daily PICU rounds. Data obtained did not affect the participant's routine care nor was it used in the clinical management of opioid tapering.

Data collection timing occurred daily, for up to 7 days, between 10 AM and 4 PM during times of routine care in order to allow a consistent time point from the previous day's opioid dosing changes and avoid the usually busy early morning clinical rounds. The exact time was negotiated with the bedside nurse in order to minimize any potential disruption of routine care. At the time of study enrollment, the following data from the electronic medical record (EMR) and bedside flow sheet were collected: medications received within the past 24 hours, data to calculate opioid cumulative dose (in MEK) peak opioid dose (in MEK), and number of days of opioid exposure prior to study enrollment demographic data (age, race, gender, admission diagnosis, weight in kilograms).

Data collection for the opioid taper rate occurred each day for up to 7 days. We collected opioid dose information given over the past 24 hours (8a to 8a). All opioids were converted to MEK. The sum of the MEKs was recorded as the MEK/day.

Data collection for the WAT-1(Fig1) began with a review of the EMR and flow sheet for the previous 12 hours followed by direct observation for 2 minutes and then a 1 minute progressive stimulus observation. During the direct observation data was collected on state, tremor, sweating, uncoordinated/repetitive movements and yawning or sneezing. Next, the patient was observed during the 1 minute progressive stimulus. During the 1 minute progressive stimulus observation, data on muscle tone and startle

to touch was collected. Finally, the patient was observed for up to 5 minutes to assess time to recovery post stimulus. The WAT-1 was measured daily for up to 7 days. With the exception of 4 observations, all WAT-1 measurements were collected by the same investigator. Training for the second evaluator consisted of didactic review of the tool and its use followed by simultaneous WAT-1 assessments with the primary investigator. Once agreement was met on how to use the WAT-1, the second investigator was allowed to obtain data independently using the WAT-1.

Data Analysis

Demographic variables were summarized and measures of central tendency (mean, median) and dispersion (standard deviation, range) were calculated on continuous data, and frequency and counts were computed on categorical data.

Descriptive statistics (means and standard deviations) were used to address the first study aim. Individual variable scores and total WAT-1 scores were recorded. For the second aim distributions of all study variables were examined to determine the need for transformations. The opioid duration and cumulative opioid dose data were skewed therefore log transformations were done to stabilize the variance and make the distributions more normal. These transformed values were used in all analyses.

Correlational analyses were used to examine the relationship among opioid withdrawal signs and symptoms (WAT-1), and opioid tapering rate, opioid exposure (log cumulative opioid dose, peak opioid dose, log duration of opioid exposure), and the child's age.

Plots were produced to describe the change in individual symptoms over time and the relationship between average opioid dose and average total WAT-1 score over time.

Mixed effect repeated models were used to determine if the changes in the WAT-1

score over study days 1 to 7 were due to 1) log opioid duration, 2) log cumulative opioid dose, 3) age, 4) gender, 5) race, 6) LOMV and 7) ICU LOS. For every comparison performed in this study, the significance level was set at $p<0.05$.

RESULTS

Participants

Twenty-eight patients met inclusion criteria. Since two families declined participation, twenty-six (93% of those eligible) were enrolled in the study. One participant who was on Extracorporeal Membrane Oxygenation (ECMO) was excluded at analysis due to his extreme cumulative opioid dose (10 fold increase over next largest value) and potentially confounding severity of illness. Thus the twenty-five participants had a mean age of 6.7 years (79.8 months) and were primarily male and white (Table 1). The majority (n=21) were enrolled from the Pediatric Intensive Care Unit and respiratory illness, trauma and post-operative management were the most common admission diagnoses. Most (n=19) were ventilated and the median duration of mechanical ventilation for those ventilated was 8.5 days (IQR=5 – 18.5 days) (Table 1). Median length of opioid duration was 8 days (IQR=5 – 15.5 days) (Table 3). Opioid taper rates varied widely from an average daily dose reduction of 24.4 MEK between observation days 1 and 2 to an increase of 14.05 MEK between days 1 and 2 (Table 4).

Signs and symptoms of opioid withdrawal

A total of 155 WAT-1 observations were performed in 25 participants over the 7 day study period. Of the 25 participants, 18 had observations for all 7 days. No participant had a daily WAT-1 total score greater than 7 (possible score 0-12). For the 25 participants 11(44%) had a WAT-1 score of greater than or equal to 3 on any given

day, indicating presence of opioid withdrawal. Of these 11, 6 (55%) were White and were males (56%). Only one participant had a rating greater than 5 (WAT-1 score =7), and 54% did not have opioid withdrawal (WAT-1 score < 3).

The most common symptoms noted over all days were diarrhea (35%), sweating (25%) fever (21%), and vomiting (20%) (Table 2). Peak occurrence of symptoms, that is, highest WAT-1 score, was noted on day 2 (mean=2). The days with the least occurrence of symptoms were day 6 and day 7 (Table 2).

Opioid Withdrawal, Exposure and Tapering

The second study aim included an examination of the relationship between signs of opioid withdrawal and opioid exposure (opioid duration, cumulative opioid dose, peak opioid dose). Participant median duration of opioid exposure was 8 days and ranged from 5 to 15.5 days (Table 3). Eight (73%) participants with opioid withdrawal had longer than 9 days duration of opioid treatment prior to tapering. There was a positive relationship between log opioid duration and the maximum WAT-1 score that approached significance ($r=0.38$, $p=0.06$). Similarly, there was a positive relationship approaching significance between opioid duration and the average WAT-1 for days 1 through 7 ($r=0.33$, $p=0.10$). The effect of opioid duration on the total WAT-1 was compared across days 1 to 7 using mixed models repeated measures ANOVA and no significant differences among the days were found ($F(1,24)=2.46$; $p=0.13$). Median cumulative opioid exposure was 49.12 MEK (IQR= 16.6-124.6) over time. We found that all (100%) participants with opioid withdrawal ($WAT-1 \geq 3$) had cumulative opioid doses greater than 2.5 MEK. There was no relationship between the cumulative opioid dose and the maximum WAT-1 ($r=0.29$, $p=0.15$), or the average WAT-1 ($r=0.22$, $p=0.28$). In

addition, no significant differences was found between days for average WAT-1 ($F(1,25)=1.09$; $p=0.313$). Median peak opioid exposure prior to taper was 9.8 MEK (IQR=16.6-124.6). Peak opioid dose was not related to the average WAT-1 ($r=0.28$; $p=0.17$) or the maximum WAT-1 ($r=0.17$; $p=0.42$).

Although in general a steady reduction in opioid dose during the tapering process is suggested, we found wide variability in opioid dose changes (tapering or increases) each day. Opioid dose changes included both tapering and increases in 22 (88%) participants over the study days. The remaining 3(12%) patients had opioid doses that only decreased each day (Figure 2). In addition, variability in dose was most severe during the first 2-3 days of the taper process, leveling off during days 4 through 7.

Opioid Withdrawal and Other Factors

Demographic data included gender, race, LOMV, ICU LOS and age. For these variables, the only effect noted was between age and peak opioid dose ($r=-0.41$; $p=0.04$). The effect of these variables on the total WAT-1 was compared across days 1 to 7 using mixed models repeated measures ANOVA. There was no significant effect of age ($F(1,23)=1.30$; $p=0.27$), gender ($F(1,24)= 0.00$; $p=0.99$), race ($F(1,24)= 2.66$; $p=0.12$), ICU LOS($F(1,20)= 0.56$; $p=0.46$) or LOMV ($F(1,18)=2.42$; $p=0.14$) on the total WAT-1 across days 1 to 7.

DISCUSSION

This prospective, descriptive observational study described the occurrence of signs and symptoms of opioid withdrawal in critically ill children undergoing opioid taper. In addition, the relationship among opioid withdrawal signs and symptoms, opioid exposure, opioid taper rate, and the child's age was examined.

Signs and Symptoms of Opioid Withdrawal

The most common symptoms (sweating, diarrhea, vomiting, fever) found in our study were similar to previous studies.^{3,7,13} Franck³ and Ista¹⁷ found in critically ill children that sleeplessness, fever, diarrhea, tremors and pupil dilation were the most common. Since our withdrawal tool did not include an evaluation of sleeplessness, or pupil dilation, comparisons to our study cannot be made.

We found a low incidence of opioid withdrawal with only half of the sample having opioid withdrawal on any given day. Prior to study implementation, staff perception of the incidence of opioid withdrawal led us to expect a higher incidence. Also, our findings are lower than those noted by Frank et al.⁷ in the original WAT-1 validation study (44% vs. 64%). In addition our findings showed little variability in severity of symptoms in those who had opioid withdrawal. That is, the level of symptoms was not high and very few subjects scored greater than 5 on any given day (WAT-1 score ranges 0 to 12). Since tapering regimens often vary among practitioners¹⁴ we anticipated varied practice with a resulting wider range of withdrawal signs and symptoms in our study as well.

Although opioid taper rate did not affect withdrawal symptoms, we found a wide variation in opioid tapering practice among the pediatric critical care providers at our institution. For example, some practitioners tapered opioid doses by 30-60% per day, while others used a more conservative approach (5-20% taper per day). Further, opioid rescue doses were not used in a consistent manner; i.e. prescribed when one or multiple withdrawal signs or symptoms were present; rather than using a symptom threshold for treatment initiation. Even though our sample differed from Franck et al.⁷

with longer durations of exposure (8 vs. 6 days) and higher peak opioid doses (9.8 MEK vs. 7.6 MEK), the resulting level of withdrawal symptoms was similar. Differences in severity of illness and opioid management may account for these findings. Individual practitioners may vary in their definition of optimal level of sedation and analgesia, opioid type and use of opioid sparing adjuvant medications. However our participants' cumulative opioid dose (49.1 MEK vs. 48.2 MEK) was similar to that found by Franck et al.⁷

Opioid Exposure

Since withdrawal signs and symptoms may be affected by both opioid dose (cumulative and peak) as well as duration, we included these in our measure of opioid exposure. Similar to other studies, peak opioid dose did not affect opioid withdrawal. Previous studies have found a similar relationship between cumulative dose and opioid withdrawal. In a prospective study conducted by Katz et al. (1994), 23 infants (<23 months) were observed for signs of opioid withdrawal post opioid exposure.²⁰ They found the occurrence of opioid withdrawal increased as cumulative dose ($p<0.005$) length of exposure ($p<0.0001$) increased. Other studies conducted in children have found a similar dose dependent relationship.^{9,21,26} In a prospective, multiple case study (n=27), Ducharme and colleagues found, in PICU patients (age 0-19 years), that as opioid peak dose increases, occurrence of withdrawal also increases, although the association was weak ($r=0.34$; $p<0.05$).⁹ The majority of pediatric literature has been conducted in a neonatal or infant population. In a retrospective study of neonates, Arnold and colleagues found a cumulative dose of 1.6mg/kg or greater to be associated with the development of opioid withdrawal.²⁶ Similar to others, our findings suggest that

as duration of exposure increases, risk of opioid withdrawal increases. However, we did not find a relationship between cumulative dose and opioid withdrawal. In the existing literature on opioid withdrawal in children, only our study and Franck's^{7,23} have used a validated pediatric opioid withdrawal instrument.

We found that increases in cumulative dose may also increase the potential for opioid withdrawal (Figure 2). Several pediatric studies had similar findings. In a prospective, descriptive opioid withdrawal study of critically ill children (<25 months), French and Nocera found a significant correlation between cumulative fentanyl dose (≥ 5.6 MEK) and opioid withdrawal score ($r=0.76$; $p<0.01$).²¹ Ducharme and colleagues found a moderate association between opioid duration and occurrence of opioid withdrawal ($r=0.41$; $p<0.01$).⁹ Katz et al. found that a duration of 5 days or more of fentanyl exposure was 50% predictive of opioid withdrawal.²⁰ French and Nocera found a significant correlation between duration of fentanyl exposure and opioid withdrawal score ($r=0.70$; $p<0.05$).²¹ In a prospective, repeated measures design study of critically ill children ($n=79$; ages 0 to 16 years), Ista and colleagues found a significant correlation between duration of opioid exposure and severity of opioid withdrawal ($r=0.52$; $p<0.001$). Similar to our study, these researchers found a dose dependent relationship between duration of opioid exposure to opioid withdrawal. Our results in conjunction with the previous findings, lead to our recommendation of use of an assessment based tapering regimen for all patients deemed at risk for opioid withdrawal by nature of their history of duration of opioid exposure (>5days) and cumulative opioid dose (>2.5 MEK).

Opioid taper rate

There is little empirical evidence to guide the practice of opioid tapering.^{1,9,10,20} Although some theoretical recommendations exist in the literature,^{18,31} few data based guidelines have been tested in the pediatric population. Of those that have been tested, no guideline was associated with a 0% incidence of opioid withdrawal signs and symptoms. In this study, we found no significant relationship between opioid taper rate and incidence of opioid withdrawal. Given the non-linear variation in overall pattern of opioid taper in our patients, we were unable to detect an association between opioid taper rate and occurrence of opioid withdrawal. Since the majority of subjects were tapered using methadone, the longer and variable half-life may have confounded the relationship between opioid taper rate and subsequent increase in WAT-1 score.

Age

Given the inherent physical developmental differences in children, age-related differences in the incidence of opioid withdrawal may be expected. At this time, few studies have investigated age-related differences in the development of opioid withdrawal. The wide age range of our sample is similar to several previous studies.^{1,13,17} However none of these studies reported age related differences in the incidence or presentation of opioid withdrawal. Only Franck et al. has evaluated the effect of age on opioid withdrawal signs and symptoms in children.^{7,20} Using a sample of children 7 months to 10 years of age, Franck⁷ found a higher incidence of vomiting in the 0 to 2 years of age group (12.3%) compared to the >6 years age group (3.2%). In addition, children greater than 6 years of age (6.1%) had lower incidence of yawning and sneezing than the 2.1 to 6 year group (13.4%). We found no relationship between age and average WAT-1 score. Since the majority of the previous studies as well as this

study are limited by small sample sizes, the possibility that age related symptom differences do exist cannot be ruled out.

Similarly to Katz et al.²⁰, our findings revealed no association between age and incidence of opioid withdrawal. Although Franck found some age related differences in the original WAT-1 validation study⁷, our study did not have similar findings. Our inability to detect an association may be reflective of our small sample size. Studies with a larger sample size may more accurately reflect the developmental differences in children as they physically mature. Except for Ista^{13,17} and Franck,^{7,23} previous studies were limited by small sample sizes.

Conclusions

Knowledge of opioid withdrawal incidence and its related factors provides valuable information for proactive opioid management. For those patients with a longer duration of exposure, the clinician should have a heightened awareness of the potential for opioid withdrawal and hence the need for a tapering regimen. In conjunction with an appropriate tapering regimen, use of a validated pediatric opioid withdrawal tool is essential in the effective assessment and management of opioid withdrawal.

Individualized, assessment based tapering regimens may lead to a shorter length of stay. Future evaluations of taper regimens using opioids with shorter half-lives may identify associations between taper rate and occurrence of opioid withdrawal.

Inappropriate management of opioid withdrawal has the potential to increase cost due to use of unnecessary laboratory or radiological diagnostic testing.

Several limitations should be considered when interpreting our findings. The generalizability of our findings is hampered by the small sample and use of a single site.

The heterogeneity of the participants' medical conditions may have confounded our results. Evaluation of the effect on opioid withdrawal was limited by the low variability of total WAT-1 scores, which may be reflective of the unexpected conservative tapering practices and other medications may have interfered with appearance of opioid withdrawal. Further, clinicians were often aware that their patient was enrolled in the study, which may have led to treatment bias. In addition, since the clinicians did not make their treatment decisions using a validated assessment tool, the possibility of over diagnosis is real. The change in tapering practices styles on any given day further contributed to potential confounding variables for this study. Future studies evaluating the use of an assessment based tapering protocol would be clinically useful. Although symptoms of opioid and benzodiazepine withdrawal overlap, not all symptoms of benzodiazepine withdrawal are addressed by the WAT-1 such as insomnia and seizures.¹⁹ Based on our findings and the findings in similar studies, we agree that opioid tapering regimens should consider risk factors, such as opioid duration. Whether other factors, such as age, affect withdrawal is not completely clear. However it is clear that to successfully identify and manage opioid withdrawal symptoms, use of a valid tool is imperative. Therefore, tolerance to the tapering regimen should be assessed daily using a validated pediatric assessment tool.

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Table 1. Participant Characteristics (n=25)

Variable	Mean	SD^b	Range
Age (mo.) ^a	79.8	61.2	7 to 214
	Median	IQR^c	Range
LOMV ^d (days)	8.5	5 to 18.5	0 to 35
ICU LOS ^e (days)	13	7.5 to 21.5	1 to 38
	Count	Percent	
Gender			
Male	16	64%	
Female	9	36%	
Race			
Asian	1	4%	
Black	12	48%	
White	11	44%	
Other	1	4%	
Ethnicity			
Hispanic	1	4%	
Non-Hispanic	24	96%	
Admission Diagnosis			
Trauma	4	16%	
Respiratory	7	28%	
Post-op ^f	5	20%	
Sepsis	3	12%	
Other	6	24%	

^amo. = months; ^bSD = Standard Deviation; ^cIQR- interquartile range; ^dLOMV= Length of Mechanical Ventilation; ^eICU LOS = Intensive Care Unit Length of Stay; ^fPost-op= Postoperative

Table 2. WAT-1 Individual Variable Scores and Total Daily WAT-1 Score (Means and Standard Deviations) ^a

Symptoms	Day 1 (N=25) Mean (SD)	Day 2 (N=25) Mean (SD)	Day 3 (N=24) Mean (SD)	Day 4 (N=21) Mean (SD)	Day 5 (N=21) Mean (SD)	Day 6 (N=21) Mean (SD)	Day 7 (N=18) Mean (SD)
Loose watery stools	0.38 (0.49)	0.36 (0.49)	0.33 (0.48)	0.33 (0.48)	0.43 (0.51)	0.29 (0.46)	0.33 (0.49)
Vomiting/retching/ gagging	0.2 (0.41)	0.24 (0.44)	0.29 (0.46)	0.29 (0.46)	0.1 (0.3)	0.05 (0.22)	0.17 (0.38)
Temperature >37.8°C	0.24 (0.44)	0.36 (0.49)	0.25 (0.44)	0.19 (0.4)	0.24 (0.44)	0.14 (0.36)	0.17 (0.38)
State	0.16 (0.37)	0.08 (0.28)	0.13 (0.34)	0.14 (0.36)	0.14 (0.36)	0 (0)	0.06 (0.24)
Tremor	0.12 (0.33)	0.12 (0.33)	0.21 (0.42)	0.05 (0.22)	0.05 (0.22)	0.05 (0.22)	0.06 (0.24)
Sweating	0.12 (0.33)	0.32 (0.48)	0.25 (0.44)	0.43 (0.51)	0.29 (0.46)	0.19 (0.4)	0.22 (0.43)
Uncoordinated/ repetitive movement	0.08 (0.28)	0.12 (0.33)	0 (0)	0.05 (0.22)	0.1 (0.3)	0.1 (0.3)	0.11 (0.32)
Yawning or sneezing	0.08 (0.28)	0.04 (0.2)	0.13 (0.34)	0.05 (0.22)	0.05 (0.22)	0.05 (0.22)	0.06 (0.24)
Startle to touch	0.2 (0.41)	0.12 (0.33)	0.08 (0.28)	0.19 (0.4)	0.14 (0.36)	0.1 (0.3)	0.06 (0.24)
Muscle tone	0.52 (1.8)	0.12 (0.33)	0.13 (0.34)	0.05 (0.22)	0.14 (0.36)	0.1 (0.3)	0.11 (0.32)
Time to gain calm state	0.08 (0.28)	0.08 (0.28)	0.08 (0.28)	0 (0)	0.05 (0.22)	0.1 (0.44)	0 (0)
Total WAT-1 score Mean (SD)	1.8 (1.47)	2 (1.68)	1.96 (1.58)	1.7 (1.45)	1.76 (1.64)	1.14 (1.28)	1.28 (1.02)

^a WAT-1 = Withdrawal Assessment Tool-1. All items scored 0-1 except for time to gain calm - 0-2 points. Total WAT-1 score is the sum of all items (0-12).

Table 3. Opioid Exposure

Variable	Median	IQR^a	Range
Opioid Duration (days)	8.0	5.0 – 15.5	5.0 – 22.0
Cumulative Opioid Dose (MEK) ^b	49.1	16.6 – 124.6	3.8 – 364.3
Peak Opioid Dose (MEK)	9.8	3.0 – 16.8	0.7 – 34.6

^aIQR= Interquartile Range

^bMEK= Morphine Equivalents per Kilogram

Table 4. Opioid Taper (n=25)

Opioid Change	N^a	Median (MEK)^b	IQR^c (MEK)	Range (MEK)
Day 1 to 2	25	-0.5	-3.20 – -0.05	-24.4 – 14.1
Day 2 to 3	24	-0.24	-0.73 – 0.07	-16.2 – 1.6
Day 3 to 4	24	-0.07	-0.64 – 0.15	-2.6 – 1.1
Day 4 to 5	24	0.0	-0.34 – 0.54	-3.6 – 2.5
Day 5 to 6	22	0.0	-0.73 – 0.06	-3.8 – 2.9
Day 6 to 7	22	-0.23	-0.94 – 0.0	-3.7 – 2.0

^aN= Sample Size

^bMEK= Morphine Equivalents per Kilogram

^cIQR= Interquartile Range

Table 5. Multivariate Correlations (n=25)

	Age (months)	log Opioid Duration	Peak Opioid Dose (MEK)^a	log Cumulative Opioid Dose (MEK)	Mean Opioid Taper Rate	Mean WAT-1^b Day 1 to 7	Max (WAT-1)
Age (months)	1.00	-0.13	-0.41*	-0.40*	0.14	-0.22	-0.06
log Opioid Duration		1.00	0.64***	0.67***	0.23	0.33	0.38
Peak Opioid Dose (MEK)			1.00	0.83***	-0.21	0.28	0.17
log Cumulative Opioid Dose				1.00	-0.06	0.22	0.29
Mean Opioid Taper Rate					1.00	0.05	0.21
Mean WAT-1 Day 1 to 7						1.00	0.83***
Max(WAT-1)							1.00

^a MEK = Morphine Equivalents per Kilogram

^b WAT-1 = Withdrawal Assessment Tool

*p < 0.05

**p < 0.01

***p < 0.001

Figure 1. WAT-1 (need to add post converting document to pdf)

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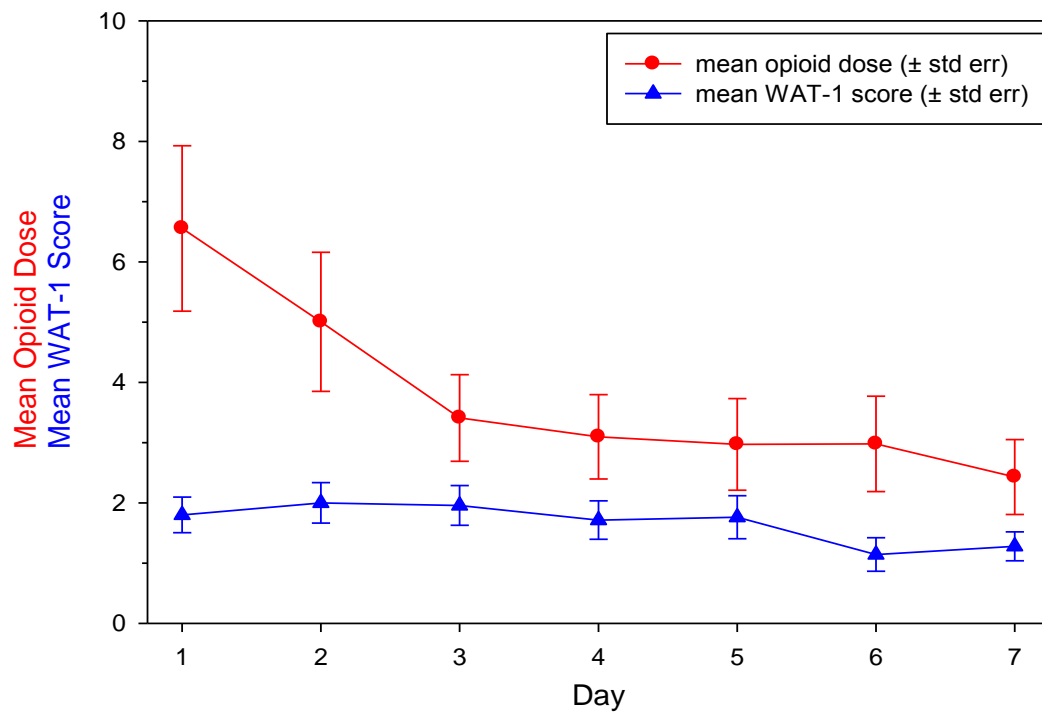


Figure 2. Mean Opioid Dose and WAT-1 Score over Time (n=25)

VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference that protocol. **NOTE: If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal.**

ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled "Special Consent Provisions." Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate "N/A."

NOTE: The Research Plan is required with ALL submissions and MUST follow the template, and include version number or date, and page numbers.

DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.

I. TITLE

Opioid withdrawal signs and symptoms in the pediatric patient during opioid tapering

II. STAFFING

A. In the table below (add additional rows as needed), indicate: (1) key project personnel including the principal investigator and individuals from other institutions, (2) their qualifications, and (3) a brief description of their responsibilities.

NAME OF INDIVIDUAL	QUALIFICATIONS	RESPONSIBILITIES
Mary Jo Grap PhD, RN, FAAN, ACNP	<ul style="list-style-type: none"> • VCU School of Nursing, Adult Health and Nursing Systems, Professor • Panel Expert in Pain Management, for the American Association of Critical-Care Nurses 	Principal Investigator
Suzanne Ameringer PhD, RN	<ul style="list-style-type: none"> • VCU School of Nursing, Assistant Professor • Expert in Pediatric Pain 	Dissertation Committee
Janet Younger PhD, RN, PNP	<ul style="list-style-type: none"> • VCU School of Nursing, Professor Emeritus • PNP and expert in Pediatrics 	Member
RK Elswick PhD	<ul style="list-style-type: none"> • VCU Biostatistician 	And Consultant
Deborah Fisher MS, RN, PNP	<ul style="list-style-type: none"> • Clinical Director Pediatric Palliative Care & Pain Management, Children's Hospital of Richmond 	Student Principal Investigator

B. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.

Prior to beginning the study, all team members will meet to establish agreement on process, duties and function. Recruitment, enrollment, data collection, data management and analysis, final report and dissemination of findings will be performed by Ms. Fisher. Dr. Ameringer and Dr. Younger will provide pediatric nursing consultation, pediatric pain consultation as well as consultation on statistical analysis and quantitative methods. Dr. Elswick will provide expert consultation for the statistical analysis portion of the study. All team members will be apprised through monthly reports via email during data collection. All team members will meet prior to data analysis and prior to final report.

III. CONFLICT OF INTEREST

Describe how the principal investigator and sub/co-investigators might benefit from the subject's participation in this project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project

Dr. Grap – no conflicts to declare
 Dr. Ameringer- no conflicts to declare
 Dr. Younger – no conflicts to declare
 Dr. Elswick – no conflicts to declare
 D. Fisher – no conflicts to declare

IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3) availability of medical or psychological resources that participants might require as a consequence of the research (if applicable), and (4) financial support.

1. Ms. Fisher will devote 6 hours per week towards conduct of this study; data collection is anticipated to take approximately 4 - 6 months.
2. Study setting is VCU Medical Center, Main 7 PICU and acute care pediatric units
3. No anticipated need for psychological resources; all participants will be under the care of a medical team
4. There is no financial support for this study

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Routine use of sedation and analgesia for ventilated children in the intensive care unit is essential for the comfort and safety of the child to protect the child from self-harm such as unplanned endotracheal extubation, anxiety related increased oxygen demand and ventilator dysynchrony.¹ However the therapeutic goal of providing adequate analgesia and sedation often results in days to weeks of continuous exposure to opioids and sedatives. Continuous exposure may result in iatrogenic opioid and sedative dependence. Few data have been published on the incidence of opioid withdrawal in the pediatric patient. The studies that have been published vary widely on incidence of opioid withdrawal (0-100%).²⁻⁵ Studies of opioid withdrawal conducted in the pediatric population have used neonatal withdrawal tools²⁻⁷ or no opioid assessment tool was used.^{3,4,8,9} The use of developmentally inappropriate instruments such as neonatal opioid withdrawal instruments may result in conclusions that are flawed. In 2008, Franck et al. developed the Withdrawal Assessment Tool-1 (WAT-1), a pediatric opioid withdrawal scale.^{9,10} At this time, the WAT-1 is the only validated pediatric opioid withdrawal assessment tool. In 2009, Ista et al. developed a promising opioid and benzodiazepine withdrawal tool, the Sophia Observation withdrawal Symptoms scale (SOS), but psychometric properties have yet to be published.¹¹ Except for the initial instrument validation studies of the WAT-1, no studies have been conducted to identify the incidence of pediatric opioid withdrawal using a validated pediatric opioid withdrawal assessment tool. In addition there is little data about factors that may affect the frequency of withdrawal signs and symptoms including opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate, severity of illness and the child's age. Therefore, the purpose of this study is to describe the frequency of opioid withdrawal signs and symptoms and to identify factors associated with these opioid withdrawal signs and symptoms.

VI. SPECIFIC AIMS

The specific aims of this study are to:

1. describe the signs and symptoms (WAT-1) of opioid withdrawal in children undergoing opioid tapering
2. examine the relationship among opioid withdrawal signs and symptoms (WAT-1), opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate, severity of illness and the child's age.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Over 90% of critically ill children receive opioids.¹² Opioids are used routinely in the pediatric intensive care population for analgesia, sedation, blunting of physiologic responses to stress, and safety.^{2,12,13} In addition, the synergistic effect of opioids in combination with benzodiazepines allows for dose reductions of both opioids and benzodiazepines.¹⁴ Continued exposure to opioids can lead to opioid dependence or tolerance. Opioid dependence is defined as a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.¹⁵ Opioid tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.¹⁵ In children, physical dependence may occur in as little as two to three days of continuous opioid therapy.¹⁶ Opioid dependence has been shown to develop even more rapidly in neonates and infants than in older children or adults.¹⁷ Once the child no longer needs the opioid or sedative, the medications are reduced over time. Since tapering routines vary among practitioners, it is not uncommon for nurses to witness signs and symptoms of opioid withdrawal in this vulnerable population.¹⁸ Opioid withdrawal signs and symptoms in adults include hiccups, goose bumps, chills, fever, tachycardia, tachypnea, hypertension, agitation, restlessness, insomnia, nausea, vomiting, diarrhea, cramps, lacrimation, rinorrhea, yawning, diaphoresis, mydriasis, bone pain, muscle aches and spasms, and seizures.¹⁶ Opioid withdrawal signs and symptoms in children include diarrhea, nausea, vomiting, fever, sweating, mottling, tremor, agitation, frequent yawning, frequent sneezing, motor disturbance, insomnia and hypertonia.^{2-6,8-11,13,18-23} Data concerning factors that affect opioid withdrawal signs and symptoms are limited. Although no studies investigating the effect of gender on withdrawal signs and symptoms have been conducted in humans, there is evidence of gender differences in opioid tolerance and incidence of withdrawal in rats. In a study conducted by Craft et al., male rats were found to have a higher withdrawal score than female rats.²⁴ In addition, there is limited data that show length of stay (LOS) in the PICU, duration of mechanical ventilation (VLOS) and cumulative opioid dosage (mg/kg) are positively associated with signs and symptoms of opioid withdrawal.^{5,13,23} Acute effects of withdrawal signs and symptoms are numerous and can be dangerous. Diarrhea and vomiting can lead to dehydration. Tachycardia may lead to unnecessary intravenous fluid resuscitation or even cardiology evaluations. Routine use of validated opioid withdrawal assessment tools or algorithms is rare.^{9,18} which may contribute to delays in diagnosis of opioid withdrawal syndrome and proper treatment. Potential long term effects of poorly managed withdrawal symptoms are unknown; however, possible consequences include prolonged tapering duration in response to attempts to alleviate withdrawal signs and symptoms as well as needless physical and emotional suffering. Of note, only one position statement on opioid withdrawal in children is available in the literature. The American Academy of Pediatrics (AAP) position statement on neonatal drug withdrawal recommends multimodal maternal screening for opioid use, enhanced recognition of signs of opioid withdrawal, routine use of appropriate opioid withdrawal tools, and medication recommendations for opioid or sedative withdrawal.²⁵ However, no such statement exists for the pediatric population.

VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

1. Survey of opioid tapering practices of pediatric healthcare providers: A national perspective.¹⁸ The purpose of this study was to describe the current opioid tapering practice of a national sample of health care providers consisting of nurse practitioners, physician assistants and physicians. Data were collected through a web based survey developed by the investigator. The 11 item survey was developed through careful review of the literature, evaluated by clinical experts in pediatric pain management and revised based on their feedback. The survey included multiple choice and open ended questions that evaluated the following: existence and use of guidelines for opioid tapering, personal preference for opioid tapering, use of expert consultation for opioid tapering, use of opioid withdrawal assessment tool, and pharmacological preference for management of signs and symptoms of opioid withdrawal. Content validity and clarity were then established by a panel of 6 pediatric providers with expertise in advanced practice nursing, medicine and survey methods. Pilot testing was conducted using 8 pediatric health care providers and further revisions made. The resulting survey was distributed to pediatric health care providers via international and national pediatric pain and palliative care email list serves. One hundred and four participants from pediatric pain and palliative care list serves responded to the survey. Of these, the majority were physicians (62%) followed by pediatric nurse practitioners (16%), clinical nurse specialists (15%), family nurse practitioners (5%), and doctors of osteopathy (2%). The majority of respondents were employed in an academic children's medical center (52%). Median age of years in pediatric practice was 16.33 years. The majority (60%) did not have a written opioid tapering protocol in their practice setting. Respondents without a protocol described regimens for opioid withdrawal that varied greatly. Approximately half (n=54) of the 104 respondents used an opioid withdrawal assessment tool. Of those using an assessment tool, the majority used the WAT-1¹³ (n=22), followed by the Finnegan

Neonatal Abstinence Score²⁶ (n=14), Clinical Opiate Withdrawal Scale²⁷ (n=6) and the Sophia Observation withdrawal Symptoms scale¹¹ (n=3). This study provided data illustrating the wide variation in opioid tapering practices among practitioners.

IX. RESEARCH METHOD AND DESIGN

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

The specific aims of this prospective, descriptive study are to 1) describe the signs and symptoms (WAT-1) of opioid withdrawal in children undergoing opioid tapering and 2) examine the relationship among opioid withdrawal signs and symptoms (WAT-1), opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), opioid taper rate, severity of illness and the child's age.

Setting

The study will be conducted in the Pediatric Intensive Care Unit (PICU), the Pediatric Progressive Care Unit (PPCU) and the acute care pediatric units at the Children's Hospital of Richmond, VCU Medical Center campus in Richmond, Virginia. The PICU, the PPCU and acute care areas, admit children with a wide range of pediatric diagnoses providing enhanced generalizability of study findings. Dr. Grap, the student's primary advisor, is an acute care nurse practitioner and researcher who has conducted numerous clinical studies in the adult intensive care units as well as one previous study in the PICU. Ms. Fisher, the student PI, is a pediatric nurse practitioner at the Children's Hospital of Richmond and has conducted one prior study in the PICU. Dr. Ameringer is an assistant professor of pediatric nursing at the VCU School of Nursing. She has conducted several clinical studies in the VCUHS pediatric units.

Table 1. Characteristics of study units from which participants will be enrolled (FY 2009)

Unit / bed #	Annual Admissions	Average LOS ^a (in days)	Average VLOS ^b (in days)
PICU/ 12	477	4.0	7.1
PPCU/ 7	348	3.2	NA ^c
Acute Care Pediatrics M7E/ 17 M7C/ 24	1991	3.9	NA ^c

^a = Length of Stay

^b = Ventilator Length of Stay

^c = Not applicable

Sample

The sample of up to 100 will be drawn from all patients, ages 2 weeks to 21 years admitted to the Children's Hospital of Richmond Pediatric Intensive Care Unit (PICU) and who have received continuous infusion opioids for greater than 5 days.^{2,5,13,21} The WAT-1 was developed for the 2 week to 18 year range.¹² Since the PICU and pediatric floors accept and treat patients up to 21 years of age, the age inclusion criteria will be adjusted to more adequately reflect the age population seen in the PICU, PPCU and pediatric acute care units. Numerous opioid withdrawal studies have found that opioid tolerance may occur after 5 days of opioid exposure.^{5,17,22} Previous studies have found that opioid withdrawal signs and symptoms are highest during taper days 1-6, therefore data collection will occur daily for up to 7 days.^{3,6,8,10,28} In order to increase external validity, we will include all admitting diagnoses. Pediatric patients (2 weeks to 21 years) from all ethnic and racial backgrounds will be recruited. Since one of the variables of the WAT-1 is restlessness, children with paralysis of one or more limbs or who are receiving neuromuscular blockers will be excluded. Should the enrolled participant be transferred to another pediatric unit (PPCU, M7C or M7E) during the up to 7 days of data collection, the student PI will continue data collection on those units. Based upon the sample size and the student PIs ability to collect data on up to 4 patients per day, a data collection period of 6 months is feasible.

Methods

Measurement of major variables

1. Opioid withdrawal signs and symptoms

Known opioid withdrawal signs and symptoms in the pediatric population include gastrointestinal (diarrhea, nausea, vomiting), autonomic (fever, sweating, mottling) and central nervous systems (tremor, agitation, frequent yawning,

frequent sneezing, motor disturbance, hypertonia).^{2-6,8-11,13,18-23} Opioid withdrawal signs and symptoms will be measured using the 11 item Withdrawal Assessment Tool – 1 (WAT-1). The WAT-1 is an 11 item pediatric opioid withdrawal instrument that includes measures of gastrointestinal (diarrhea, nausea, vomiting), autonomic (fever, sweating) and central nervous system (tremor, sedation state, uncoordinated movement, yawning or sneezing, startle to touch, muscle tone and time to gain calm) measures of opioid withdrawal.¹³ This pediatric instrument is the revised version of the original 21 item Opioid Benzodiazepine Withdrawal Scale (OBWS).¹⁰ The original instrument was tested in a pediatric critical care population (n=15 patients; 693 observations) ranging in age from 6 weeks to 28 months. The result of the original testing of the proposed 21 item OBWS (sensitivity = 50%; reliability = 87%) led to a revision of the OBWS to the 19 item WAT-1. The 19 item WAT-1 was tested in a pediatric critical care population (n=83; 1040 observations) ranging in age from 6 months to 10 years. Redundant signs and symptoms and symptoms with low levels of association with withdrawal intensity ratings were eliminated resulting in the current recommended 11 item tool.¹³ The WAT-1 (Appendix A) showed superior psychometric properties (sensitivity = 87%; specificity = 88%) compared to the initial testing of the OBWS (sensitivity = 50%; specificity= 80%; IRR=0.8). Although inclusion criteria for the validation of the WAT-1 ranged from 2 weeks to 18 years, the actual sample ranged from age 6 months to 10 years. Since the WAT-1 is validated only for the 6 month to 10 year age group, children aged <6 months or >10 years will be excluded. The WAT-1 includes the State Behavioral Scale (SBS) which was originally validated for assessment of pre and post stimulus state (Appendix B).¹ The SBS was designed to evaluate the young patient's response to a progressive stimulus. Negative numbers reflect levels of sedation. Positive numbers reflect levels of agitation. A score of zero reflects neither agitation nor sedation. "The progressive stimulus used in the SBS assessment provides a standard stimulus for observing signs of withdrawal."¹ Since the SBS is a subscale of the WAT-1 score, it will be completed along with each WAT-1 measurement.

2. Opioid exposure

Opioids are used routinely in the pediatric intensive care population in order to reduce pain, anxiety and morbidity. Continuous infusion of both an opioid (fentanyl) for analgesia and a benzodiazepine (midazolam) for sedation is routine practice in the PICU for all mechanically ventilated infants and children. Given the synergistic effects of benzodiazepines and opioids, the addition of an opioid has been associated with up to 50% dose reductions of midazolam.²⁹ Fentanyl is preferred to morphine since it releases less histamine, thus decreasing the associated hypotension.¹⁹ Numerous clinical studies have found that the duration of opioid receptor occupancy is related to the development of opioid tolerance.^{7,10,30,31} In a prospective study conducted by Katz et al (1994), 23 infants (<23 months) were observed for signs of opioid withdrawal post opioid exposure.⁵ They found a positive correlation of dosage (p<0.005) and length of exposure (p <0.0001) on occurrence of opioid withdrawal. In fact, a dose of 2.5mg/kg fentanyl or more than 9 days exposure was 100% predictive of withdrawal. Since withdrawal signs and symptoms may be affected by both opioid dose (cumulative and peak) as well as duration, in this study opioid exposure will consist of all of these factors.

Opioid Dose (Cumulative and Peak). In a prospective study of infants ranging in age from 1 week to 22 months , Katz, Kelly & His found that a total dose of 1.5mg/kg was associated with a 50% rate of opioid withdrawal.⁵ Other studies conducted in children have found a similar dose dependent relationship.^{4,6,17} In a prospective, multiple case study (n=27), Ducharme and colleagues examined the effects of variable opioid taper rates on occurrence of opioid withdrawal on PICU patients (age 0-19 years), there was a minimal correlation between opioid peak dose and occurrence of withdrawal (r = 0.34; p <0.05).⁴ In a prospective, descriptive opioid withdrawal study of critically ill children (< 25 months), French and Nocera found a significant correlation between cumulative fentanyl dose and opioid withdrawal score (r = 0.76; p<0.01).⁶ In a retrospective study of neonates, Arnold and colleagues found a total dose of 1.6mg/kg to be associated with the development of opioid withdrawal.¹⁷ There was no significant difference in peak opioid dose between the neonates who had opioid withdrawal and those infants with no signs or symptoms of opioid withdrawal. Because the literature shows some relationship between cumulative and peak opioid dose on occurrence of opioid withdrawal, opioid dose will be described as both cumulative and peak. Peak dose will be determined by calculation of daily opioid dose. To compare analgesics across types, all opioids can be converted to a common drug (i.e. morphine) and reported as morphine equivalents per kilogram (MEK).^{8,21} For this study, fentanyl conversion to morphine will be calculated by the formula 10mg of IV morphine = 0.1mg IV fentanyl.³² Morphine equivalents will be divided by the patient's body weight to determine MEK. Peak and cumulative MEK will be calculated pretaper and daily at 10am during taper. All opioids will be converted to morphine equivalents per kilogram (MEK). Daily dose of MEK will be calculated. The largest daily MEK will be recorded as the peak opioid dose. Cumulative dose will be determined by summation of daily MEKs prior to initiation of opioid taper.

Opioid Duration. Previous studies in children have found a correlation between opioid duration prior to taper with occurrence of opioid withdrawal signs and symptoms.^{4,6,21} Ducharme and colleagues found a moderate association

between opioid duration and occurrence of opioid withdrawal ($r = 0.41$; $p < 0.01$).⁴ Katz, Kelly & Hsi found that a duration of 5 days or more of fentanyl exposure was 50% predictive of opioid withdrawal.⁵ French and Nocera found a significant correlation between duration of fentanyl exposure and opioid withdrawal score ($r = 0.70$; $p < 0.05$).⁶ In a prospective, repeated measures design study of critically ill children ($n = 79$; ages 0 to 16 years), Ista and colleagues found a significant correlation between duration of opioid exposure and severity of opioid withdrawal ($r = 0.52$; $p < 0.001$).²¹ Opioid duration will be calculated as the number of days of continuous or scheduled opioid exposure prior to initiating opioid taper. Children with at least 5 days of opioid exposure will be eligible for the study.

3. Opioid taper rate

The goal of tapering opioids is to safely wean the opioid from the patient while avoiding the incidence of opioid withdrawal. There is little empirical evidence to guide the practice of opioid tapering.^{4,8-10} Although some recommendations exist in the literature, few recommended guidelines have been tested in the pediatric population.^{2,4,7,8,10,30,31} Berens et al. (2006) conducted a double-blinded, randomized control trial using methadone and found a 20% incidence of need for rescue medications to treat signs and symptoms of opioid withdrawal.² Of those that have been tested, no guideline was associated with a 0% incidence of opioid withdrawal signs and symptoms.^{4,7-10,30}

A recent survey of international pediatric pain management providers conducted by Fisher found a wide variation in opioid tapering practice (see preliminary study #1). Opioid tapering practices were divided into two categories: conservative or aggressive. 69 % of practitioners in the study used a conservative method, defined as tapering reduction of 20% or less per day. 12 % used a more aggressive method, greater than 20% dose reduction per day. Within each category, tapering practices varied. Reported conservative regimens ranged from 10% reductions per week to 10% every day. Aggressive regimens varied from 30% every 2 days to 50% per day. Since rates of taper vary depending on clinician, opioid tapering rate will be defined as percentage change in total opioid dose per day, expressed in morphine equivalent units per kilogram (MEK) of the child's body weight. Nonscheduled opioids that are administered will also be included in the daily opioid tapering rate calculation. In addition, medications that may alleviate withdrawal signs and symptoms such as benzodiazepines, α -adrenergic (clonidine, dexmedetomidine), antiemetics and antipyretics will be recorded. Although several studies recommended opioid dose reductions ranging from 10-20% per day, none of the studies resulted in an absence of opioid withdrawal signs and symptoms.^{2,4,7,10,30,31} At this point in time, there is no gold standard for opioid tapering in children.

4. Severity of Illness Severity of illness is used to further describe the population and has been included in previous pediatric opioid withdrawal studies.^{2,13,21} In a prospective, randomized trial comparing the effect of a 5 day methadone taper versus a 10 day methadone taper on incidence and severity of opioid withdrawal, the investigators no difference in severity of illness in either group. In the prospective psychometric evaluation of the WAT-1, severity of illness was included only as a demographic characteristic.¹³ Similarly, Ista and colleagues included severity of illness only as a demographic characteristic.²¹ Given the pervasive nature of opioid withdrawal signs and symptoms on multiple systems including the central nervous system, autonomic nervous system and gastrointestinal system, a potential relationship between severity of illness and opioid withdrawal signs and symptoms is possible. In addition, severity of illness may impact the individual child's need for analgesics and sedatives. To our knowledge, this study would be the first to examine the relationship between severity of illness and frequency of signs and symptoms of opioid withdrawal. The revised Pediatric Index of Mortality (PIM2) will be used to measure severity of illness.³³ The PIM-2 (Appendix C) has been used to measure severity of illness in cardiac surgery patients,³⁴ severe head injury,³⁵ medical surgical,³⁶ and multidisciplinary PICU populations.³⁷ The PIM2 will be measured, based on data from the previous 24 hours, at time of study enrollment.

5. Age. Few studies have evaluated the effect of age on opioid withdrawal signs and symptoms.^{5,13} Katz and colleagues found no correlation between age and incidence of opioid withdrawal.⁵ Franck found some age related differences in incidence of specific opioid withdrawal signs and symptoms.¹³ For example, there was a higher incidence of vomiting in the 0-2 year age group (12.3%) compared to the >6 years age group (3.2%). Age, in months, will be measured at the time of study enrollment.

6. Additional Demographics

Other demographic data (race, gender, hospital admission diagnosis, length of mechanical ventilation, ICU length of stay) will be collected to describe the sample.

Table 2:Key study variables and their measurement

Variable	Measure	Measurement Interval
Opioid withdrawal signs and symptoms	WAT-1 (0-12)	Daily at same time for 7 days
Opioid exposure Opioid dose	Peak opioid dose (in MEK) Cumulative opioid dose (in MEK)	Once at time of study enrollment Once at time of study enrollment
Opioid duration	Number of days of opioid exposure	Once at time of study enrollment
Opioid taper rate	opioid mg/kg per day (MEK per day)	Daily for 7 days
Severity of Illness	Pediatric Index of Mortality (PIM2)	Once at time of study enrollment
Age	Age in months	Once at time of study enrollment
Additional demographic data	Race, gender, admission diagnosis, weight in kilograms, length of mechanical ventilation (days), ICU length of stay (days)	Once at time of study enrollment – ICU LOS may not be available at time of enrollment

Note. WAT-1 = Withdrawal Assessment Tool -1. MEK = Morphine equivalents per kilogram

Procedure:

Prior to beginning the study, the student PI will provide an informational inservice to the pediatric nursing leadership and staff of the involved units (PICU, PPCU, M7C & M7E). The student will identify patients who meet selection criteria through daily rounds on the PICU. Since this is a descriptive study, there will be no change in the medical plan of the participants. No more than minimal risk is anticipated. Data obtained will not affect the participant's routine care nor will it be used in the clinical management of opioid tapering. Waiver of assent is being requested since the intended participants will be sedated during the observation period. Permission will be obtained from the parent/legal guardian at time of study enrollment.

Should the child awaken during the data collection time period, the student investigator will debrief them on the study. Data collection timing will occur each afternoon between 10 AM and 4 PM during times of routine care in order to allow a consistent time point from the previous day's opioid dosing changes and avoid the usually busy early morning clinical rounds. The exact time will be negotiated with the bedside nurse in order to minimize any potential disruption of routine care. Data collection will occur daily for up to 7 days. Decisions about individual opioid therapy for these subjects including opioid duration and dosage will be made by the medical team.

At the time of study enrollment, the student PI will collect the following data from the electronic medical record (EMR) and bedside flowsheet: medications received within the past 24 hours, data to calculate opioid cumulative dose (in MEK) peak opioid dose (in MEK), and number of days of opioid exposure prior to study enrollment demographic data (age, race, gender, admission diagnosis, PIM2, weight in kilograms)

Data collection for the opioid taper rate will occur each day for up to 7 days. The student PI will collect opioid dose information given over the past 24 hours (8a to 8a). All opioids will be converted to MEK. The sum of the MEKs will be recorded as the MEK/day. The MEK/day will be compared to the previous day's MEK/day and the percentage reductions per day will be calculated.

Data collection for the WAT-1 will begin with a review of the EMR and flowsheet for the previous 12 hours, as per the WAT-1 instructions. The student PI will then record incidence of any symptom listed on the WAT-1 including temperature >37.8 C, vomiting/wretching/gagging and loose/watery stools. Next, the student will observe the participant undisturbed for 2 minutes, during which time data will be collected on several variables of the WAT-1 scale: state (SBS), tremor, sweating, uncoordinated/repetitive movements and yawning or sneezing. Next, the student PI will observe the patient during a progressive stimulus. The progressive stimulus will entail first calling the participant's name in a calm voice. If the participant does not respond, then the student PI will call the participant's name and gently touch the arm or leg. If the participant does not respond, the student PI will observe the patient during a planned noxious procedure such as endotracheal suctioning or turning, which will be performed by the bedside nurse. During the 1 minute stimulus observation, the student PI will collect data on muscle tone and startle to touch. The WAT-1 will be measured similarly daily for up to 7 days.

Should a participant transfer to the progressive (PPCU) or acute care pediatric (M7C & M7E) units, the student PI

will continue to collect data on the new unit until either completion of 7 days of data collection or hospital discharge.

X. PLAN FOR CONTROL OF INVESTIGATIONAL DRUGS, BIOLOGICS, AND DEVICES.

For investigational drugs and biologics: IF IDS is not being used, attach the IDS confirmation of receipt of the management plan.. See item #11 on Initial Review form.

For investigational and humanitarian use devices (HUDs): Describe your plans for the control of investigational devices and HUDs including: (1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s); (2) plan for storing the investigational product(s)/ HUD as specified by the sponsor (if any) and in accordance with applicable regulatory requirements; (3) plan for ensuring that the investigational product(s)/HUDs are used only in accordance with the approved protocol; and (4) how you will ensure that each subject understands the correct use of the investigational product(s)/HUDs (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

NA

XI. DATA ANALYSIS PLAN

For investigator-initiated studies.

Demographic variables will be descriptively summarized. Measures of central tendency (mean, median) and dispersion (standard deviation, range) on continuous data, and frequency and count on categorical data will be computed as appropriate.

The first aim of the study (specific aim #1) is to describe the signs and symptoms of opioid withdrawal (WAT-1) in children undergoing opioid tapering. Descriptive statistics (means and standard deviations) will be used.

The second aim (specific aim #2) is to examine the relationship among the maximum opioid withdrawal signs and symptoms (WAT-1), opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure) summed to day of maximum amount, opioid taper rate (range of percentage changes), severity of illness (PIM2) and the child's age. In order to account for variance of opioid choice amongst practitioners, all opioids will be converted to morphine equivalents. Distributions of all study variables will be examined to determine the need for transformations. Multiple regression will be performed to evaluate the relationship among opioid withdrawal signs and symptoms (WAT-1), and opioid tapering rate (range of percentage changes), opioid exposure (cumulative opioid dose, peak opioid dose, duration of opioid exposure), and the child's age.

XII. DATA AND SAFETY MONITORING

- **If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.**
- **If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.**
- **If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at <http://www.research.vcu.edu/irb/wpp/flash/X-2.htm>**

The research involves no more than minimal risk. Since this is an observational study, there will be no change in the medical plan of the participants. Data obtained will not affect the participant's routine care nor will it be used in the clinical management of opioid tapering. Data will be entered into an electronic record. Access to this password protected site will be limited to the student investigator. Data will be shared only with the investigators listed on this research plan during monthly study meetings.

XIII. MULTI-CENTER STUDIES

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project,

describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

NA

XIV. INVOLVEMENT OF NON-VCU INSTITUTIONS/SITES (DOMESTIC AND FOREIGN)

1. Provide the following information for each non-VCU institution/site (domestic and foreign) that has agreed to participate:

- Name of institution/site
- Contact information for institution/site

NA

2. For each institution, indicate whether or not it is “engaged” in the research (see OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>.)

NA

3. Provide a description of each institution’s role (whether engaged or not) in the human subjects research, adequacy of the facility (in order to ensure human subject safety in the case of an unanticipated emergency), responsibilities of its agents/employees, and oversight that you will be providing in order to ensure adequate and ongoing protection of the human subjects. You should only identify institutions that have agreed to participate. If additional institutions agree to participate at a later time, they must be added by amendment to the protocol.

NA

4. For each institution that is “engaged” provide an OHRP Federalwide Assurance (FWA) # if: (1) the research is not exempt, AND (2) the research involves a DIRECT FEDERAL award made to VCU (or application for such).

NOTE: Additional guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm>, and <http://www.research.vcu.edu/irb/wpp/flash/XVII-11.htm>.

NA

XV. INVOLVEMENT OF INDEPENDENT INVESTIGATORS

INDEPENDENT INVESTIGATOR: an individual who is acting independently and not acting as an agent or employee of any institution or facility while carrying out his or her duties in the research protocol. Additional guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-15.htm>.

ENGAGEMENT IN RESEARCH: An independent investigator becomes "engaged" in human subjects research when he/she (i) intervenes or interacts with living individuals for research purposes; or (ii) obtains individually identifiable private information for research purposes [45 CFR 46.102(d)-(f)]. See OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>.

1. Provide a list of independent investigators.

2. For each independent investigator indicate whether or not he/she is “engaged” or “not engaged” in the research

3. For each independent investigator who is “engaged”: (1) describe his/her role with human subjects/identifiable

human data, AND (2) describe YOUR oversight of his/her involvement.

NA

NOTE: If an independent investigator is “engaged,” and the research is (1) not exempt AND (2) involves a DIRECT FEDERAL award made to VCU (or application for such), the independent investigator must sign a formal written agreement with VCU certifying terms for the protection of human subjects. For an agreement to be approved: (1) the PI must directly supervise all of the research activities, (2) agreement must follow the ORSP template, (3) IRB must agree to the involvement of the independent investigator, AND (4) agreement must be in effect prior to final IRB approval.

XVI. HUMAN SUBJECTS INSTRUCTIONS (Be sure to use the sub-headings under A-I) – you will need to update all this when ALL the previous sections are finalized .. I am not going to review this until all that is OK ...

ALL sections of the Human Subjects Instructions must be completed with the exception of the section entitled “Special Consent Provisions.” Complete that section if applicable.

A. DESCRIPTION

Provide a detailed description of the proposed involvement of human subjects or their private identifiable data in the work.

Data will be obtained from the electronic medical record and direct observation of the participant. Data will include: opioid withdrawal score (WAT-1), opioid taper rate (total dose of opioid per day in MEK), medications, pretaper peak MEK, pretaper cumulative MEK, number of days of exposure to opioids prior to taper, age of participant, gender, race, diagnosis, weight (for use in calculation of MEK).

The participants in this study will be observed only in this descriptive study. The observation period of 7 minutes for data collection is anticipated to be minimally intrusive and should not affect clinical care since the timing of daily data collection will be negotiated with the bedside nurse to be conducted during times of routine nursing care.

B. SUBJECT POPULATION

Describe the subject population in terms of sex, race, ethnicity, age, etc., and your access to the population that will allow recruitment of the necessary number of participants. Identify the criteria for inclusion or exclusion of any subpopulation and include a justification for any exclusion. Explain the rationale for the involvement of special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. If you plan to allow for the enrollment of Wards of the State (or any other agency, institution, or entity), you must specifically request their inclusion and follow guidance on Wards and Emancipated Minors in the VCU IRB Written Policies and Procedures (specifically WPP#: XV-3) available at <http://www.research.vcu.edu/irb/wpp/flash/XV-3.htm>.

Participant recruitment will occur at the Children’s Hospital of Richmond, VCU Health System campus. The 7th floor Pediatric floor will be the site of all participant recruitment. All pediatric patients (ages 2 weeks to 21 years) who have received continuous infusion opioids for >5 days will be included in recruitment efforts. Patients will not be excluded for race, sex, or ethnicity. Access to the population will be facilitated by the student PI who is a Pediatric Nurse Practitioner employed by the Children’s Hospital of Richmond. Participants will be recruited over a 6 month data collection period.

C. RESEARCH MATERIAL

Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

Data will be obtained from the Electronic Medical Record (EMR), bedside flowsheet and observation. Once the data has been entered on computer, only code numbers will be associated with all forms and materials. Only the investigators will have access to the data. Once the participant is enrolled in the study, demographic data will be collected from the EMR. Existing data (see list below) that is not obtained at enrollment will be obtained daily for up to 7 days. Length of

mechanical ventilator days and ICU length of stay will be calculated at discharge from the PICU. Research data (see list below) will be obtained daily for up to 7 days.

Existing data- Cerner medication orders, demographic information (age, gender, weight) , length of mechanical ventilation days (VLOS), ICU length of stay

Research data –

Collected daily -WAT-1, opioid taper rate (total MEK per day)

Collected at time of study enrollment- calculation of PIM2, calculation of peak opioid (MEK) dose and opioid cumulative dose (MEK) plus duration (in days) of opioid exposure prior to initiation of opioid taper.

D. RECRUITMENT PLAN

Describe in detail your plans for the recruitment of subjects including: (1) how potential subjects will be identified (e.g., school personnel, health care professionals, etc), (2) how you will get the names and contact information for potential subjects, and (3) who will make initial contact with these individuals (if relevant) and how that contact will be done. If you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable, describe any special recruitment procedures for these populations.

Participants will be recruited from a pediatric intensive care population within a 12 bed unit. Notification of ongoing study will be provided via laminated flier in each room. Potential participants will be identified by the student investigator through daily discussion with PICU health care professionals. The student investigator will make initial contact with the potential participants at the time of enrollment. At the time of initial contact, the student investigator will explain the study, answer questions and obtain permission from the parent or legal guardian.

E. POTENTIAL RISKS

Describe potential risks whether physical, psychological, social, legal, or other and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

Since the study is observational, there will be no change in standard of care. Breach of confidentiality and invasion of privacy are potential risks. Likelihood of occurrence is minimal.

F. RISK REDUCTION

Describe the procedures for protecting against or minimizing potential risk. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects.

The bedside nurse will inform the student PI when routine care (assessments, vital signs) will be delivered, so that no additional participant stimulation will occur. Parents or legal guardians of participants will be given a copy of the permission form. All forms and materials will be stored in a locked cabinet in a locked room. All forms will be coded with an assigned participant number. All data entered on computer will be linked to the participant number. Participant identifiers will be destroyed on entering data on computer. Data analysis will be reported in aggregate.

G. ADDITIONAL SAFEGUARDS IF ANY PARTICIPANTS WILL BE VULNERABLE

Describe any additional safeguards to protect the rights and welfare of participants if you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. Safeguards to protect the rights and welfare of participants might relate to Inclusion/Exclusion Criteria: (“Adults with moderate to severe cognitive impairment will be excluded.” “Children must have diabetes. No normal controls who are children will be used.”) Consent: (“Participants must have an adult care giver who agrees to the participant taking part in the research and will make sure the participant complies with research procedures.”

“Adults must be able to assent. Any dissent by the participant will end the research procedures.”) **Benefit:**
 (“Individuals who have not shown benefit to this type of drug in the past will be excluded.”).

Legal guardians of participants must give permission for enrollment of participant in study. The student investigator has expertise in working with young infants and children.

Exclusion criteria:

No infants less than 2 weeks of age will be included; no children older than 21 years will be included. Since one of the variables of the WAT-1 is restlessness, children with paralysis of one or more limbs or who are receiving neuromuscular relaxants will be excluded.

Since this is a descriptive study, no change in medical plan is anticipated.

H. CONFIDENTIALITY

Describe how the confidentiality of data collected as part of this project will be protected including pre-screening data (e.g., physical controls on the data; access controls to the data; coding of data; legal controls, such as a Federal Certificate of Confidentiality; statistical methods; or reporting methods).

Each participant will be assigned a number for this descriptive study. All data will be safeguarded by storage in a password protected electronic file. Only the student investigator will have access. Only the researchers listed on this research plan will be shown the data. Since the data obtained will be de-identified and the data will be reported in aggregate for the final report and publications, it will not be possible to identify any individual participant.

I. PRIVACY

Describe how the privacy interests of subjects will be protected where privacy refers to persons and their interests in controlling access to themselves, and assess their likely effectiveness. Identify what steps you will take for subjects to be comfortable: (1) in the research setting and (2) with the information being sought and the way it is sought.

1. If the child is awake during data collection, the student PI will establish rapport with the participant. The student investigator has over twenty years experience as a pediatric nurse- including over 7 years experience as a PICU nurse.
2. All efforts to remain unobtrusive will be attempted during data collection of asleep participants
3. The student PI will collaborate with the bedside nurse on timing of data collection in order to respect the comfort and privacy of the participant. No personal data will be collected or recorded. All data collected will be stored in a password protected database.

J. RISK/BENEFIT

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If a test article (investigational new drug, device, or biologic) is involved, name the test article and supply the FDA approval letter.

This is not a treatment study. There are no direct benefits from participation in the study. Since this is an observational study, no more than minimal risk is anticipated. Potential benefits of this study include addition of empirical evidence to the sparse fund of literature on the subject of opioid tapering in children. To the best of the investigator's knowledge, this will be the first observational study measuring signs and symptoms and severity of opioid withdrawal in children using the recently validated opioid withdrawal instrument – WAT-1. Predicted long term benefit of the study data will be eventual translation of the knowledge into clinical decision-making that ensures optimal assessment based management of opioid withdrawal in children.

K. COMPENSATION PLAN

Compensation for subjects (if applicable) should be described, including possible total compensation, any proposed bonus, and any proposed reductions or penalties for not completing the project.

No compensation will be offered

L. CONSENT ISSUES

1. CONSENT PROCESS

Indicate who will be asked to provide consent/assent, who will obtain consent/assent, what language (e.g., English, Spanish) will be used by those obtaining consent/assent, where and when will consent/assent be obtained, what steps will be taken to minimize the possibility of coercion or undue influence, and how much time will subjects be afforded to make a decision to participate.

The parent/legal guardian will be asked to provide permission for those children <18 years of age. For those patients aged 18 to 21 years, the Legal Authorized Representative (LAR) will be approached for consent. The student PI will obtain permission using the English language. The parent/ legal guardian will be approached for permission when the student PI has identified that the child will meet study inclusion criteria within 24 hours. The permission will be obtained at the bedside when possible. Explanation of the study will be provided in writing and verbally. The parent/legal guardian will be offered a hard copy of the permission to review overnight. Since the child will be receiving sedatives and analgesics, waiver of assent is requested.

2. SPECIAL CONSENT PROVISIONS

If some or all subjects will be cognitively impaired, or have language/hearing difficulties, describe how capacity for consent will be determined. Please consider using the VCU Informed Consent Evaluation Instrument available at <http://www.research.vcu.edu/irb/guidance.htm>. If you anticipate the need to obtain informed consent from legally authorized representatives (LARs), please describe how you will identify an appropriate representative and ensure that their consent is obtained. Guidance on LAR is available at <http://www.research.vcu.edu/irb/wpp/flash/XI-3.htm>.

NA

3. If request is being made to **WAIVE SOME OR ALL ELEMENTS OF INFORMED CONSENT FROM SUBJECTS OR PERMISSION FROM PARENTS**, explain why: (1) the research involves no more than minimal risk to the subjects, (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practicably be carried out without the waiver or alteration; **AND** (4) whether or not subjects will be debriefed after their participation. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XI-1.htm>. **NOTE: Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below).**

NA

4. If request is being made to **WAIVE DOCUMENTATION OF CONSENT**, provide a justification for waiver based on one of the following two elements **AND** include a description of the information that will be provided to participants: (1) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Subject will be asked whether they want documentation linking them with the research, and each subject's wishes will govern; or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-2.htm

NA

5. If applicable, explain the **ASSENT PROCESS** for children or decisionally impaired subjects. Describe the procedures, if any, for re-consenting children upon attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm> and <http://www.research.vcu.edu/irb/wpp/flash/XVII-7.htm>.

NA

6. If request is being made to **WAIVE THE REQUIREMENT TO OBTAIN ASSENT** from children age 7 or higher, or

decisionally impaired subjects, explain why: (1) why some or all of the individuals age 7 or higher will not be capable of providing assent based on their developmental status or impact of illness; (2) the research holds out a prospect of direct benefit not available outside of the research; AND/OR (3) [a] the research involves no more than minimal risk to the subjects, [b] the waiver or alteration will not adversely affect the rights and welfare of the subjects, [c] the research could not practicably be carried out without the waiver or alteration; AND [d] whether or not subjects will be debriefed after their participation. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm>

1. All children participating in this study will be critically ill and on sedatives and opioids hence will not be capable to provide assent. 3. [a]The research is an observational study that will not impact daily care of the child. [b] this waiver will not adversely affect the rights and welfare of the child, [c] the research could not be practicably carried out without the waiver [d] should the child awaken enough to understand, the child will be debriefed after their participation. (1)The researcher anticipates that the children enrolled in this study will be sedated and possibly unconscious during the initial opioid tapering efforts, thus, it would be inappropriate to approach the patient for assent. (2) no direct benefit is anticipated for the patients during the study. (3) [a]the non-experimental descriptive and correlational research involves no more than minimal risk to the participants [b] the waiver will not adversely affect the rights and welfare of the participants [c] the research could not practicably be carried out without waiver [d] where applicable, subjects may be debriefed after participation at the time the legal guardian(s) are debriefed.

7. If request is being made to waive consent for emergency research, see guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-16.htm>.

NA

8. If applicable, address the following issues related to **GENETIC TESTING**:

a. FUTURE CONTACT CONCERNING FURTHER GENETIC TESTING RESEARCH

Describe the circumstances under which the subject might be contacted in the future concerning further participation in this or related genetic testing research.

NA

b. FUTURE CONTACT CONCERNING GENETIC TESTING RESULTS

If planned or possible future genetic testing results are unlikely to have clinical implications, then a statement that the results will not be made available to subjects may be appropriate. If results might be of clinical significance, then describe the circumstances and procedures by which subjects would receive results. Describe how subjects might access genetic counseling for assistance in understanding the implications of genetic testing results, and whether this might involve costs to subjects. Investigators should be aware that federal regulations, in general, require that testing results used in clinical management must have been obtained in a CLIA-certified laboratory.

NA

c. WITHDRAWAL OF GENETIC TESTING CONSENT

Describe whether and how subjects might, in the future, request to have test results and/or samples withdrawn in order to prevent further analysis, reporting, and/or testing.

NA

d. GENETIC TESTING INVOLVING CHILDREN OR DECISIONALLY IMPAIRED SUBJECTS

Describe procedures, if any, for consenting children upon the attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired.

NA

e. CONFIDENTIALITY

Describe the extent to which genetic testing results will remain confidential and special precautions, if any, to protect

NA

References:

1. Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med* 2006;7:107-14.
2. Berens RJ, Meyer MT, Mikhailov TA, et al. A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. *Anesth Analg* 2006;102:1045-50.
3. Carnevale FA, Ducharme C. Adverse reactions to the withdrawal of opioids and benzodiazepines in paediatric intensive care. *Intensive Crit Care Nurs* 1997;13:181-8.
4. Ducharme C, Carnevale FA, Clermont MS, Shea S. A prospective study of adverse reactions to the weaning of opioids and benzodiazepines among critically ill children. *Intensive Crit Care Nurs* 2005;21:179-86.
5. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med* 1994;22:763-7.
6. French JP, Nocera M. Drug withdrawal symptoms in children after continuous infusions of fentanyl. *J Pediatr Nurs* 1994;9:107-13.
7. Robertson RC, Darsey E, Fortenberry JD, Pettignano R, Hartley G. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. *Pediatr Crit Care Med* 2000;1:119-23.
8. Pederson C, Parran L. Opioid tapering in hematopoietic progenitor cell transplant recipients. *Oncol Nurs Forum* 2000;27:1371-80.
9. Parran L, Pederson C. Effects of an opioid taper algorithm in hematopoietic progenitor cell transplant recipients. *Oncol Nurs Forum* 2002;29:41-50.
10. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. *Intensive Crit Care Nurs* 2004;20:344-51.
11. Ista E, van Dijk M, de Hoog M, Tibboel D, Duivenvoorden HJ. Construction of the Sophia Observation withdrawal Symptoms-scale (SOS) for critically ill children. *Intensive Care Med* 2009;35:1075-81.
12. Marx CM, Rosenberg DI, Ambuel B, Hamlett KW, Blumer JL. Pediatric intensive care sedation: survey of fellowship training programs. *Pediatrics* 1993;91:369-78.
13. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med* 2008;9:573-80.
14. Richman PS, Baram D, Varela M, Glass PS. Sedation during mechanical ventilation: a trial of benzodiazepine and opiate in combination. *Crit Care Med* 2006;34:1395-401.
15. Definitions Related to the Use of Opioids for the Treatment of Pain 2001. (Accessed October 14, 2010, at <http://www.ampainsoc.org/advocacy/opioids2.htm>.)
16. McGuire DB, Yarbro CH. *Cancer pain management*. Orlando: Grune & Stratton; 1987.
17. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hersenson MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology* 1990;73:1136-40.
18. Fisher D. A survey of opioid tapering practice in children. *In*; 2010.
19. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med* 2000;28:2122-32.
20. Dewey WL. Various factors which affect the rate of development of tolerance and physical dependence to abused drugs. *NIDA Res Monogr* 1984;54:39-49.
21. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. *Crit Care Med* 2008;36:2427-32.
22. Anand KJ, Arnold JH. Opioid tolerance and dependence in infants and children. *Crit Care Med* 1994;22:334-42.

23. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. *Crit Care Med* 1999;27:196-9.
24. Craft RM, Stratmann JA, Bartok RE, Walpole TI, King SJ. Sex differences in development of morphine tolerance and dependence in the rat. *Psychopharmacology (Berl)* 1999;143:1-7.
25. Neonatal drug withdrawal. American Academy of Pediatrics Committee on Drugs. *Pediatrics* 1998;101:1079-88.
26. Finnegan LP, Connaughton JF, Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis* 1975;2:141-58.
27. Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. *Drug Alcohol Depend* 2009;105:154-9.
28. Norton SJ. Aftereffects of morphine and fentanyl analgesia: a retrospective study. *Neonatal Netw* 1988;7:25-8.
29. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998;35:37-47.
30. Lugo RA, MacLaren R, Cash J, Pribble CG, Vernon DD. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. *Pharmacotherapy* 2001;21:1566-73.
31. Siddappa R, Fletcher JE, Heard AM, Kielma D, Cimino M, Heard CM. Methadone dosage for prevention of opioid withdrawal in children. *Paediatr Anaesth* 2003;13:805-10.
32. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med* 2002;347:1094-103.
33. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med* 2003;29:278-85.
34. Czaja AS, Scanlon MC, Kuhn EM, Jeffries HE. Performance of the Pediatric Index of Mortality 2 for pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2010.
35. Grinkeviciute DE, Kevalas R, Saferis V, Matukevicius A, Ragaisis V, Tamasauskas A. Predictive value of scoring system in severe pediatric head injury. *Medicina (Kaunas)* 2007;43:861-9.
36. Wolfler A, Silvani P, Musicco M, Salvo I. Pediatric Index of Mortality 2 score in Italy: a multicenter, prospective, observational study. *Intensive Care Med* 2007;33:1407-13.
37. Hariharan S, Merritt-Charles L, Chen D. Risk-adjusted outcome evaluation in a multidisciplinary intensive care unit. *West Indian Med J* 2007;56:240-5.

Curriculum Vitae
Deborah Fisher, PhD, RN, CS, PNP-BC, CPON

PERSONAL INFORMATION

Present Titles: Clinical Director, Pediatric Palliative Care & Pain Management,
Children's Hospital of Richmond; Nursing Research Facilitator, Virginia
Commonwealth University, Richmond, VA

Address:

Office: Children's Hospital of Richmond
Virginia Commonwealth University Health Systems
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Richmond, VA 23298
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Citizenship: USA

LICENSURE

- RN, State of Virginia, valid through 9-30-11
- Pediatric Nurse Practitioner, State of Virginia, valid through 9-30-11
- Certificate to Prescribe Pharmaceuticals, State of Virginia, expires 9-30-11

EDUCATION

Institution	Degree	Major	Date
Virginia Wesleyan College,	B.A.	Biology	May 1985
Virginia Commonwealth University	B.S.	Nursing	May 1987
Virginia Commonwealth University	M.S.	Child Health.	December 1996
Virginia Commonwealth University	PhD	Nursing	May 2012

SPECIALTY AND SUBSPECIALTY CERTIFICATION

- Certified as a Pediatric Nurse Practitioner (PNP) by the American Association of Critical Care Nurses Certification Corporation in February 2001; recertification effective through 3-31-17, Certification # 0276201-06
- Certified as a Pediatric Oncology Nurse by the Oncology Nursing Certification Corporation in April 2003; recertification effective through 12-31-15

PROFESSIONAL EXPERIENCE

Institution / Agency	Position	Date
Virginia Commonwealth University School of Nursing	Adjunct Faculty NUR 345 Nursing of Children	3/06 to present Fall 2006 Spring 2007 Fall 2007
VCU Health Systems	Nursing Research Facilitator	3/09 to present
Children's Hospital of Richmond/ VCU Health Systems	Clinical Director Pediatric Palliative Care & Pain Management	11/05 to present
VCU Health Systems / Medical College of Virginia Hospitals	Pediatric Nurse Practitioner Hematology Oncology	6/97 to 11/05
Medical College of Virginia Hospitals	PICU Hourly Staff	5/95 to 10/01
Henrico Doctor's Hospital Richmond, VA	PICU Hourly Staff	7/95 to 10/01
Children's National Medical Center Washington, D.C.	NICU/PICU Float Pool Traveling Nurse	3/95 to 6/95
Southwest Texas Methodist Hospital San Antonio, TX	PICU Staff - Traveling Nurse	12/94 to 3/95
Tulane Medical Center New Orleans, LA	PICU Staff - Traveling Nurse	9/94 to 12/94
California Pacific Medical Center San Francisco, CA	NICU Staff - Traveling Nurse	7/94 to 8/94
Santa Barbara Cottage Hospital Santa Barbara, CA	NICU Staff - Traveling Nurse	3/94 to 6/94
Children's Hospital of Oakland Oakland, CA	PICU Staff - Traveling Nurse	1/93 to 3/94
Medical College of Virginia Hospital Richmond, VA	PICU Staff	10/91 to 11/93

Chippenham Hospital Richmond, VA	Maternal Child Nursing Float Pool	6/90 to 9/92
Kimberly Quality Care Richmond, VA	Pediatric Home Health RN	4/90 to 10/93
Palomar Hospital Escondido, CA	Pediatric Traveling Nurse	2/90 to 4/90
Medical College of Virginia Richmond, VA	Infants and Toddlers Floor RN	6/87 to 2/90

PUBLICATIONS

Original Contributions- Peer Reviewed Journals

Fisher, D. & Sawin, K. (1998). Latex allergy in the primary care setting. Journal for the American Academy of Nurse Practitioners, 10(5), 203-208.

Fisher, D. (1998). Latex allergy: development of a resource manual. Journal of Pediatric Health Care, 12(5), 263-264.

Fisher, D. (2010). Opioid tapering in children: A review of the literature. Advanced Critical Care Nursing(21)2; 139-145.

Arif, M., **Fisher, D.** & Matsuda, Y. (2010). Biobehavioral measures for pain in the pediatric patient. Pain Management Nursing. (in press)

Unpublished Manuscripts

Arif-Rahu, M., **Fisher, D.** Matsuda, Y. (in press). Biobehavioral measures for pain in the pediatric patient. Pain Management Nursing. ASPMN (in press)

Ameringer, SW., **Fisher, D.**, Sreedhar, S., McKinney-Ketchum, J., & Yanni, L. The effectiveness of a pediatric pain management module in medical students. Journal of Palliative Medicine. (in press)

Fisher, D. & Ameringer, S. Survey of opioid tapering practices in pediatric providers : A national perspective.

Fisher, D., Grap, MJ, Ameringer, S., Younger, J. & Elswick, R.K. Signs and Symptoms of Opioid Tapering in Children.

Book Chapters

Tyler, MK & **Fisher, D.** (2006) Pediatric Palliative Care. In Advanced Practice Nurses Guidelines for Credentialing. Hospice and Palliative Care Nurses Association: Pittsburgh, PA.

Fisher, D. & V. Lucas. (2010) Skin. In Guidelines for Pediatric Palliative Care (1st ed.). Association of Pediatric Oncology Nurses and Children's Oncology Group., (contributing author)

RESEARCH

Internally Funded by Virginia Commonwealth University Health Systems

2011. Mentor. *Effect of a Security System on Perception of Safety for Nurses on a Psychiatric Unit*

2010-2011. Mentor. *Development of an Alcohol Withdrawal Assessment Tool.*

2011. Mentor. *A Retrospective Review of Time to Antibiotic Administration in the Pediatric Patient.*

2010. Student Principal Investigator. *Signs and Symptoms of Opioid Withdrawal in Children Undergoing Opioid Withdrawal*

2010. Student Principal Investigator. *Survey of Opioid Tapering Practices in Pediatric Providers.*

2009. Co -Principal Investigator (multicenter study). *Effects of Healthy Work Environment on Graduate Nurse Role Transition and Retention*

2010. Mentor. *Study on the Use of Radiofrequency (RF) Safety Systems Comparing Advanced Platform to Existing Systems (SURFSCAPES)*

2006. Principal investigator. *Development of a Pediatric Pain Assessment Tool*

Partial or Fully Funded; Corporate Sponsors/Organizations

2009. Co-investigator: Development of and Initial Testing of an Online Pediatric Pain Curriculum (CChange: \$25,000)

PROFESSIONAL INVITATIONS

Invited Presentations/Panel Discussions/Lectures; non VCUHS:

“Pain Management Across the Ages”. Podium Presentation. VCNP Pharmacology Conference. Lewis Ginter Botanical Gardens, Richmond, VA October 9, 2010

“Neonatal Palliative Care: Putting Quality into Your Day”. Podium Presentation. Greensboro, NC, September 28, 2009.

“Opioid Tapering in Children: a review of the literature”. Podium presentation. AAHPM/HPNA annual meeting. Boston, MA March 4, 2010

HCAP: Helping Children of Adult Patients; A Pediatric Palliative Care Service; Poster Presentation. AAHPM/HPNA Annual Assembly. Tampa, Florida, February 2008

“Pediatric Palliative Care”. Pediatric Grand Rounds. Mary Washington Hospital. June 12, 2007

“Hematopoiesis”. Central Virginia Association of Neonatal Nurses. Richmond, VA. November 9, 2005.

Boo boos, Ouchies and Other Owies. Mary Washington Hospital. November 13, 2007

Symptom Management. Pediatric Palliative Care. ELNEC-PPC conference for nurses. May 1, 2004 .Children’s National Medical Center. Association of Pediatric Oncology Nurses.

Symptom Management. Pediatric Palliative Care. ELNEC-PPC conference for nurses; June 2005. Georgetown University. Washington, DC

Symptom Management. Pediatric Palliative Care. ELNEC-PPC conference for nurses; April 9, 2010 Washington D.C.; Children’s National Medical Center/District of Columbia Pediatric Palliative Care Consortium

Pediatric Pain Case Studies. Georgetown University Health Systems. May 17, 2011. Washington, D.C.;

VCUHS Sponsored Professional Invitations:

“Latex allergy”. Pediatrics Core. October 22, 1998

Pediatric chemotherapy certification classes –MCV-1998-1999.

Adult and Pediatric chemotherapy certification classes – MCV- 1999- 2001

Facilitator for Pediatric Hematology Oncology Core –MCV-July 13, 2000

“Overview of the Hematologic System”. Pediatric Hematology Oncology Core. July 13, 2000

Pediatric Pain Inservices. Nursing inservices –MCV-2001 – present (taped- requirement for all new pediatric nurses hired)

Central Venous Catheters. Resident Noon Lecture series. October of 1999, 2000, 2001; July 2002; July 14, 2003; August 13, 2004

Facilitator for Pediatric End of Life Resident Noon Lecture series. 2001, 2002, 2003, 2004, 2005, 2006, 2007

Bugs, Bugs, Everywhere. Survival Skills for School Nurses. Virginia Museum of Fine Arts- August 2002

“Fever, Neutropenia & Sepsis”. Pediatric Oncology Core. –MCV-May 7, 2002

Omas... and other Pediatric Cancers. Inservice radiology nurses September 11, 2003; Inservice pediatric nurses 2003, April 27, 2005; NUR 649 November 14, 2005.

“Pain Management for Children”. Hematology Core Class for Parents. October 10, 2003

“Anatomic and Physiologic Differences between Adults and Children”. Pediatric Clinical Byte. –VCUMC- October 23, 2003

Infants. Pediatric Clinical Byte. –VCUMC-October 23, 2003

End of Life Care for Children. Nursing 649 VCU School of Nursing. December 1, 2003; October 4, 2004; November 14, 2005

Pediatric Pain Management. Nursing 649 VCU School of Nursing November 14, 2005.

Boo boos, Ouchies and Other Owies. Pediatric Clinical Byte. September 22, 2005; pediatric resident noon conference; September 23, 2005

Symptom Management. Pediatric Palliative Care. ELNEC conference for nurses. March 17, 2005(VCUMC/ Association of Pediatric Oncology Nurses); October 6, 2005(VCUMC); September 8,2006(VCUMC); September 17, 2007; October 10,2008 (VCUMC); October 20,2010 (VCUMC)

Pain Management. Pediatric Palliative Care, ELNEC conference for nurses. September 18, 2007; October 9,2008 (VCUMC); October 9, 2009 (VCUMC);October 21, 2010(VCUMC)

Research.... Pediatric Hematology Oncology Core #1. VCUMC April 15,2005

Pediatric Palliative Care. Bereavement Coordinators Meeting. VCUMC. March 7, 2006.

Care of the Child at the Time of Death. Pediatric Resident Lecture. May 24, 2006

Principles of Palliative Care. Perinatal/Neonatal Palliative Care Conference. October 2, 2006

Achieving Quality Palliative Care- ELNEC Core conference for nurses. January 24, 2007; ELNEC Critical Care, November 2, 2007; ELNEC Critical Care, Richmond VA, December 4, 2009.

Introduction to Pediatric Palliative Care. Nursing Pediatric Palliative Care Core. March 13, 2007

Ethics panel discussion: Futile treatment. Keynote Presentation.Trauma Nursing Symposium; The Trauma Nursing Spectrum: Beyond the Cutting Edge. Richmond Convention Center. April 30, 2007

Pediatric Pain Management. Noon conference. August 30, 2007

Case studies in Pediatric Palliative Care. Pediatric Palliative Care Core #2. October 9, 2007

Pain Management in the Pediatric Population. NRP Best Practices Seminar. January 15, 2008

Pediatric Pain Case Studies. NRP Best Practices Seminar. March 10, 2008

Pediatric Pain Case Studies- cognitive impairment. July 10, 2008

VCU School of Nursing Guest Lectures

Pediatric Lab Interpretation – Anemia. November 2001,2002; October 9, 2003. VCU SON NUR 511

Pain Management in Children. Nursing 345. VCU School of Nursing. February 22, 2008.

Pediatric Hematology. Nursing 345. VCU School of Nursing. April 4, 2008.

Pediatric Oncology. Nursing 345. VCU School of Nursing. April 4, 2008.

EOL care in children. Nursing 345. VCU School of Nursing. April 11, 2008

Omas... and other Pediatric Cancers. ; NUR 649 November 14, 2005

Nursing Care of the Child and Family at the End of Life. Nursing 410 VCU School of Nursing. December 5, 2003

MEMBERSHIP IN HONORARY AND PROFESSIONAL SOCIETIES

National Association of Pediatric Nurse Associates & Practitioners 1997 - present

National Association of Pediatric Nurse Associates & Practitioners – Virginia

Chapter

- Public Relations Chair 1999-2001
- President 2001-2002

Virginia Council of Nurse Practitioners 1996 - present

Pediatric Oncology Group - contributing member 1997 – 2000

Children’s Oncology Group – full member 2000- 2006

Association of Pediatric Oncology Nurses 2000 – present

Sigma Theta Tau – Omega Chapter 2003 – present

- Vice President 2003 to 2005

Noah’s Children – Pediatric Hospice Board member; Education subcommittee 2003 to present

Children’s Hospice International 2005 to 2008

Hospice and Palliative Care Nurses Association -2005 to present

American Society for Pain Management Nursing- 2006 to present

Southern Nursing Research Society – 2008 to present

American Pain Society – 2011 to present

Manuscript Reviewer for Journals or Textbooks

Ad Hoc Reviewer. Heart and Lung. 2011

HONORS / AWARDS

Barbara Farley Scholarship, awarded for leadership to graduate student, VCUHS Week of the Nurse 2010

HOSPITAL SERVICE

- Nursing Services Professional Practice Council 2001-2003
- Pediatric Professional Practice Council (nursing) – Chairman 2001 – 2003
- Standards of Practice Council 2002- 2003
- VCU Health Systems Pain Council 2001 - present
- Pediatric Pain Council – Chair 2001- present
- Medicine and Pediatrics Leadership Committee –2001-present
- Children’s Oncology Group End of Life Education Task Force – 2000 to 2006
- Pediatric Compassionate Care Committee – 2001 to 2004
- Discharge Task Force 1997 to 1999
- Children’s Professional Practice Council – 2001 to present
- Pediatric Nursing Conference Planning Committee – conference October 2002
- Oncology Nursing Leadership –2003 to 2005
- Oncology Nursing Education Committee – 2003 to 2005
- Pediatric Palliative Care Task Force- 2003 to 2005
- Pediatric APN Council – co-chair 2005 to 2009
- Advanced Practice Nursing steering committee- 2006 to 2007
- Nursing Research Advisory Council – co-chair – 2008 to present
- Council of Advanced Practice Nursing
 - CAPN Grand Rounds subcommittee- 2008 to 2009
 - CAPN Executive Board - 2009 to present
 - Vice Chair August 2010 to December 2011
 - Chair 2012 to present