1-1-2015

Defining Risk for Iatrogenic Withdrawal in Critically Ill Children

Kaitlin Marie Best
University of Pennsylvania, kaitlin.m.best@gmail.com

Follow this and additional works at: http://repository.upenn.edu/edissertations

Part of the Nursing Commons

Recommended Citation
http://repository.upenn.edu/edissertations/1611

This paper is posted at ScholarlyCommons. http://repository.upenn.edu/edissertations/1611
For more information, please contact libraryrepository@pobox.upenn.edu.
Defining Risk for Iatrogenic Withdrawal in Critically Ill Children

Abstract
Humane care for critically ill pediatric patients supported on mechanical ventilation necessitates comfort management that includes sedation therapy. Critically ill patients quickly become tolerant to the opioids and benzodiazepines used for sedation therapy and require increasing doses of these medications to achieve the same therapeutic effect. In turn, after recovery from their primary illnesses, rapid weaning or abrupt cessation of sedative therapy in drug tolerant patients precipitates iatrogenic withdrawal syndrome - a problem that adds to the personal and financial burden of intensive care. While numerous studies have focused on illuminating iatrogenic withdrawal syndrome symptomatology, a new perspective for addressing this preventable complication of pediatric intensive care is now warranted. This dissertation will use data from the RESTORE clinical trial [U01HL086622 and U01HL086649 (PI: Curley & Wypij); 31-center cluster randomized trial of nurse-led sedation management on clinical outcomes in children requiring mechanical ventilation for acute respiratory failure] to conduct a series of analyses comparing patient-, process- and system-level data between those subjects who developed iatrogenic withdrawal syndrome and those who did not. By exploring variables at multiple levels, this study will be the most comprehensive evaluation of iatrogenic withdrawal syndrome ever completed and will contribute new knowledge to the field. The studies will collectively answer the key question: What factors impact the development of iatrogenic withdrawal syndrome in pediatric patients recovering from critical illness? Furthermore, the relative contributions of patient, process, and systems factors will be combined to create a predictive model of patient risk for clinically significant iatrogenic withdrawal syndrome in pediatric patients recovering from critical illness. This dissertation will contextualize the phenomenon of iatrogenic withdrawal syndrome within the unique clinical circumstances in which it occurs. More importantly, risk factors identified through this study could lead to the development of personalized risk profiles and prevention protocols for vulnerable children in the pediatric intensive care unit.

Degree Type
Dissertation

Degree Name
Doctor of Philosophy (PhD)

Graduate Group
Nursing

First Advisor
Martha A. Curley

Keywords
benzodiazepine, iatrogenic withdrawal syndrome, opioid, pediatric intensive care, sedation

Subject Categories
Nursing

This dissertation is available at ScholarlyCommons: http://repository.upenn.edu/edissertations/1611
DEFINING RISK FOR IATROGENIC WITHDRAWAL IN CRITICALLY ILL CHILDREN

Kaitlin M. Best

A DISSERTATION

in

Nursing

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2015

Supervisor of Dissertation

_____________________
Martha A. Q. Curley, PhD, RN, FAAN
Ellen & Robert Kapito Professor of Nursing Science

Graduate Group Chairperson

_____________________
Connie Ulrich, PhD, RN, FAAN
Associate Professor of Nursing and Associate Professor of Bioethics, Department of Medical Ethics, School of Medicine

Dissertation Committee:
Joseph I. Boullata, PharmD, RPh, BCNSP, FASPEN, Professor of Pharmacology & Therapeutics
Jean C. Solodiuk, PhD, RN, Nurse Practitioner in Pain Treatment Services, Boston Children’s Hospital
David Wypij, PhD, Associate Professor of Pediatrics, Boston Children’s Hospital; Senior Lecturer on Biostatistics, Harvard T.H. Chan School of Public Health
DEDICATION

To Mom, Dad, and Ian – for seeing the possibilities in the impossible, and for giving me
the strength to finish this journey

And to the patients, families and clinicians who are transformed by the experience of
pediatric critical illness – for reminding me why we must always question the care we
provide and pursue innovation constantly
ACKNOWLEDGMENT

Completing this PhD thesis involved a cast of thousands, whose contributions can never be adequately acknowledged. My PhD journey began when I met Dr. Terry Richmond, who helped me to see the possibilities that the Hillman Program could offer and who has never stopped challenging me to dig deeper. She has shown me the true meaning of being a scholar, and I can only hope to live up to her example. None of this work would have been possible without the support of the Hillman Foundation, and Ahrin Mishan in particular. He has my unending gratitude for his equanimity, and his ability to see the bigger picture carried me through the transition from the BSN to PhD. I have been impressed by the scientific sophistication of my mentor, Dr. Martha Curley, since our first meeting, and it has been a privilege to grow my scholarship under her guidance. Her generosity is unparalleled, and I continue to be thankful for the opportunity to work with data from as high-caliber a trial as RESTORE. The study’s project managers, Ruth Lebet and Lou Ventura, have been exceptional colleagues over the past several years and have made me feel like part of the team in spite of my occasional ineptitude. I am indebted to them both for sharing their wisdom and time with me on countless occasions. Thank you to Dr. David Wypij and Ms. Lisa Asaro, for their patience with my inexperience, ready acceptance of my many questions, and Lisa especially for her willingness to let me look over her shoulder. My grandmother, Mary Mikkelson, made my Penn education possible and without her I never would have discovered the Hillman Program. My parents, Laura and Jerry, and partner, Ian, who put up with my moods, frustration, and venting at all hours of the day and night: your sacrifices, physical and emotional support, and editorial skills have made all the difference.

iii
RESEARCH SUPPORT

The following research was supported by:

1. The National Institutes of Health, National Institute for Nursing Research under a Ruth L. Kirschstein National Research Service Award for Pre-Doctoral Fellows in Nursing Research (F31NR015172)

2. The Office of Nursing Research at the University of Pennsylvania School of Nursing

3. The Hillman Scholar’s Program in Nursing Innovation
ABSTRACT

DEFINING RISK FOR IATROGENIC WITHDRAWAL IN CRITICALLY ILL CHILDREN

Kaitlin M. Best

Martha A. Q. Curley

Humane care for critically ill pediatric patients supported on mechanical ventilation necessitates comfort management that includes sedation therapy. Critically ill patients quickly become tolerant to the opioids and benzodiazepines used for sedation therapy and require increasing doses of these medications to achieve the same therapeutic effect. In turn, after recovery from their primary illnesses, rapid weaning or abrupt cessation of sedative therapy in drug tolerant patients precipitates iatrogenic withdrawal syndrome - a problem that adds to the personal and financial burden of intensive care. While numerous studies have focused on illuminating iatrogenic withdrawal syndrome symptomatology, a new perspective for addressing this preventable complication of pediatric intensive care is now warranted. This dissertation will use data from the RESTORE clinical trial [U01HL086622 and U01 HL086649 (PI: Curley & Wypij); 31-center cluster randomized trial of nurse-led sedation management on clinical outcomes in children requiring mechanical ventilation for acute respiratory failure] to conduct a series of analyses comparing patient-, process- and system-level data between those subjects who developed iatrogenic withdrawal syndrome and those who did not. By exploring variables at multiple levels, this study will be the most comprehensive evaluation of iatrogenic withdrawal syndrome ever completed and will contribute new knowledge to the field.
The studies will collectively answer the key question: What factors impact the development of iatrogenic withdrawal syndrome in pediatric patients recovering from critical illness? Furthermore, the relative contributions of patient, process, and systems factors will be combined to create a predictive model of patient risk for clinically significant iatrogenic withdrawal syndrome in pediatric patients recovering from critical illness. This dissertation will contextualize the phenomenon of iatrogenic withdrawal syndrome within the unique clinical circumstances in which it occurs. More importantly, risk factors identified through this study could lead to the development of personalized risk profiles and prevention protocols for vulnerable children in the pediatric intensive care unit.
TABLE OF CONTENTS

DEDICATION ..................................................................................................................... ii
ACKNOWLEDGMENT ....................................................................................................... iii
RESEARCH SUPPORT ..................................................................................................... iv
ABSTRACT ....................................................................................................................... v
TABLE OF CONTENTS .................................................................................................... vii
LIST OF TABLES ............................................................................................................... ix
LIST OF FIGURES .......................................................................................................... ix
CHAPTER 1: INTRODUCTION .......................................................................................... 1
  Background ..................................................................................................................... 3
  Context of Sedation Management in the PICU ................................................................. 5
  Tolerance ....................................................................................................................... 9
  Weaning and Iatrogenic Withdrawal Syndrome ............................................................. 12
  Assessment and Management of IWS .......................................................................... 12
  Operational Definitions ............................................................................................... 17
  Chapter Aims and Rationales ....................................................................................... 20
    Chapter 2: Specific Aims ............................................................................................ 20
    Rationale .................................................................................................................... 20
    Chapter 3: Specific Aims ............................................................................................ 21
    Rationale .................................................................................................................... 21
    Chapter 4: Specific Aims ............................................................................................ 22
    Rationale .................................................................................................................... 22
  Strengths and Limitations ......................................................................................... 23
  Significance ................................................................................................................. 24

CHAPTER 2: SYSTEMATIC REVIEW AND CONCEPTUAL MODEL ........................... 26
  Abstract ....................................................................................................................... 27
  Introduction ................................................................................................................. 29
  Methods ...................................................................................................................... 30
  Results ......................................................................................................................... 31
    Patient-Level Factors ............................................................................................... 32
    System-Level Factors ............................................................................................... 37
  Discussion ................................................................................................................... 38
  Acknowledgements .................................................................................................... 43
  Works Cited ................................................................................................................ 44
  Figures and Tables ...................................................................................................... 49

CHAPTER 3: TOLERANCE, PATTERNS OF WEANING, AND IATROGENIC
WITHDRAWAL SYNDROME ......................................................................................... 65
  Abstract ....................................................................................................................... 66
  Introduction ................................................................................................................. 68
Materials and Methods ................................................................. 69
Results .................................................................................. 74
Discussion .............................................................................. 76
Conclusion .............................................................................. 78
Acknowledgements ................................................................. 80
References ............................................................................... 81
Figures and Tables ................................................................. 84
CHAPTER 4: A PREDICTIVE MODEL OF RISK FOR IATROGENIC
WITHDRAWAL SYNDROME .......................................................... 92
Abstract ................................................................................ 94
Introduction ........................................................................... 96
Methods ............................................................................... 97
Results ............................................................................... 100
Discussion ........................................................................... 102
Acknowledgments ................................................................. 108
References ........................................................................... 110
Figures and Tables ................................................................. 115
Supplemental Methods .......................................................... 121
Supplemental Table ............................................................... 124
Supplemental References ....................................................... 125
CHAPTER 5: DISCUSSION AND CONCLUSION .................................. 126
Summary and Overall Goals .................................................... 127
Major Findings: Tolerance ...................................................... 127
Major Findings: Weaning ......................................................... 129
Major Findings: Patient-Level Risk Factors ............................ 131
Major Findings: Process-Level Risk Factors ............................ 134
Major Findings: System-Level Risk Factors ............................ 136
Limitations ............................................................................ 139
Future Directions ................................................................. 141
Conclusion ............................................................................ 144
APPENDICES ......................................................................... 145
BIBLIOGRAPHY .................................................................... 146
LIST OF TABLES

Table 2-1. Detailed search strategy........................................................................56
Table 2-2. Articles on concurrent opioid and benzodiazepine therapy ..................57
Table 2-3. Articles on opioid therapy only.............................................................61
Table 2-4. Articles on benzodiazepine therapy only .............................................63
Table 3-1. Patient characteristics by pattern of weaning ......................................86
Table 3-2. Opioid and benzodiazepine exposure pre-opioid weaning by pattern of weaning ........................................................................................................88
Table 3-3. Opioid and benzodiazepine exposure during opioid weaning by pattern of weaning .........................................................90
Table 4-1. Demographic and clinical characteristics of study sample according to IWS status ................................................................................................................116
Table 4-2. Preweaning medication characteristics according to IWS status ..........117
Table 4-3. System-level characteristics of study sample and associations with site-specific IWS rate .................................................................118
Table 4-4. Predictive models of IWS......................................................................119
Table 4-5. Predictor variables of interest ...............................................................124

LIST OF FIGURES

Figure 2-1. Systematic search and selection process ..............................................49
Figure 2-2. Proportion of subjects with IWS relative to the total number of subjects among included studies ................................................................. 50
Figure 2-3. Risk for Iatrogenic Withdrawal Syndrome (IWS). Conceptual model relating three levels of risk factors for IWS in critically ill children .................51
Figure 2-4. Cross-study comparison of duration of opioid therapy in opioid-only and mixed agent (i.e. opioid and benzodiazepine administration) studies, among subjects with IWS ...............................................................52
Figure 2-5. Cross-study comparison of duration of benzodiazepine therapy among subjects with IWS ..................................................................................53
Figure 2-6. Cross-study comparison of cumulative dose of opioids among subjects with IWS .................................................................................................54
Figure 2-7. Cross-study comparison of cumulative dose of benzodiazepines among subjects with IWS .................................................................55
Figure 3-1. Start of weaning decision algorithm ....................................................84
Figure 3-2. Opioid weaning patterns .....................................................................85
Figure 4-1. Mean daily sedation dose preweaning according to age category and IWS status ........................................................................................................115
CHAPTER 1

INTRODUCTION

The rapid evolution of pediatric intensive care over the past 40 years has been accompanied by fundamental changes in comfort management for critically ill children. Comfort care in critically ill, non-surgical pediatric patients supported on mechanical ventilation relies primarily on the use of opioids and benzodiazepines for sedation. However, tolerance to and physical dependence on the opioids and benzodiazepines used for sedation therapy can develop within a short span of time (Anand et al., 2010; Barr, McPhie-Lalmansingh, Perez, & Riley, 2011; Jenkins, 2011). During recovery from their primary illnesses, failure to gradually wean sedative therapy in physically dependent patients leads to iatrogenic withdrawal syndrome (IWS), a cluster of physiologic signs and symptoms that includes elevated temperature, tachycardia and hypertension, protracted vomiting, severe diarrhea, and seizures (Franck, Harris, Soetenga, Amling, & Curley, 2008; Franck, Scoppettuolo, Wypij, & Curley, 2012). Despite this known complication of sedation therapy, opioids and benzodiazepines are an essential pharmacologic therapy in the pediatric intensive care unit (PICU); therefore, this dissertation study explores risk factors for IWS in critically ill children, in order to further our understanding of which children are at greatest risk for experiencing this phenomenon and arm clinicians with knowledge on how best to prevent IWS.

This chapter will provide important background information regarding the clinical circumstances in which critically ill children receive PICU care and experience the use of sedative and analgesic medications, in order to provide a more complete understanding of the context in which the phenomenon of IWS occurs. Subsequent chapters will present
the three component papers that comprise this dissertation study: First, a systematic review of the available literature was undertaken in order to identify known risk factors for IWS (Chapter 2). Established and hypothesized risk factors were incorporated into a conceptual model that guided subsequent data analyses. The remaining sections of this dissertation study used data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study (U01HL086622 and U01 HL086649; PIs: Curley & Wypij), a 31-center cluster randomized trial investigating the effects of a nurse-led, goal-directed sedation management protocol on clinical outcomes in children requiring mechanical ventilation for acute respiratory failure in the PICU.

Given the key role that the rate of sedation weaning plays in the incidence of IWS, the second component of this study analyzed current patterns of weaning from sedative medications in usual practice, using data from 308 subjects enrolled during the baseline, pre-randomization phase of the RESTORE trial (Chapter 3). The findings from that analysis helped elucidate the relationships among tolerance, weaning, and IWS. Specifically, analysis of the baseline population allowed development, testing and refinement of operational definitions for tolerance and weaning that were under developed in the literature on IWS in the PICU; those definitions and identified relationships between tolerance and pattern of weaning offered important insights affecting the incorporation of those variables in later analyses.

Finally, a secondary analysis of existing data from the 2449 subjects enrolled during the intervention phase of the RESTORE trial was conducted, in order to identify statistically significant risk factors associated with the outcome of IWS (Chapter 4). By
exploring variables at several levels, this study is one of the most comprehensive evaluations of IWS to date.

The specific aims for this dissertation were as follows:

1. To identify risk factors for clinically significant IWS in pediatric patients recovering from critical illness. (CHAPTER 2)

2. To characterize patterns of weaning from opioids and/or benzodiazepines in pediatric patients recovering from critical illness, as they relate to the outcome of clinically significant IWS. (CHAPTER 3)

3. To create a predictive model of patient risk for clinically significant IWS in pediatric patients recovering from critical illness, based on the relative contributions of patient, process, and systems factors. (CHAPTER 4)

The following sections provide a comprehensive discussion of the population of patients who require sedation in the PICU, the context in which sedative medications are administered, and how these factors contribute to the development of IWS. The biological mechanisms underlying the development of tolerance, physical dependence and subsequent IWS are described. In addition, current clinical practices in assessing for and managing IWS are reviewed. This information provides the necessary baseline knowledge upon which the three studies in the remainder of the dissertation were built.

Background

Nearly 150,000 critically ill infants and children in the United States are supported on invasive mechanical ventilation in the PICU every year (Agency for Healthcare Quality and Research, 2009). Various ventilator modes have been developed
to attempt to match ventilator-delivered breaths with the child’s spontaneous efforts, but patient-ventilator asynchrony still develops and can be a source of significant discomfort (Cheifetz, 2003). Humane care for these patients necessitates comfort management, a multi-dimensional concept that addresses issues of pain, agitation, anxiety, and insomnia. Approaches to care include both non-pharmacologic and pharmacologic interventions to increase patient comfort (Anand & the International Evidence-Based Group for Neonatal Pain, 2001; Herr et al., 2006). Because of the diversity of pharmacologic agents available for comfort management, by the time the first consensus guideline on sedation management in critically ill children was released in the United Kingdom in 2006, (Stephen Playfor et al., 2006) up to 24 different medications were being used in PICUs worldwide for analgesia and sedation to facilitate mechanical ventilation (Jenkins, Playfor, Bevan, Davies, & Wolf, 2007; Twite, Rashid, Zuk, & Friesen, 2004; Vet et al., 2013).

Combination therapy, including an opioid and a benzodiazepine, is the most common strategy for sedation of patients in the PICU (Ista, van Dijk, Gamel, Tibboel, & de Hoog, 2008; Jenkins et al., 2007; Vet et al., 2013). The recommended and most commonly used medications are morphine, fentanyl and midazolam (Jenkins et al., 2007; Lasky, Ernst, & Greenspan, 2012; Twite et al., 2004). Continuous infusions of opioids, including morphine and fentanyl, have rapid analgesic effects that are useful in reducing discomfort associated with mechanical ventilation, while also helping to prevent ventilator asynchrony and working synergistically with benzodiazepines to promote sedation (Johnson, Miller, & Hagemann, 2012). Benzodiazepines are highly effective
sedatives and anxiolytics, and their amnestic effects are also valued in the PICU, where memories of mechanical ventilation and invasive procedures can have significant, long-term negative psychological effects (Colville, Kerry, & Pierce, 2008; Colville, 2008; Rennick & Rashotte, 2009; Rennick et al., 2004).

Context of Sedation Management in the PICU

Sedation for mechanical ventilation in the PICU takes place within a unique context, whose characteristics both directly and indirectly impact the effectiveness of the therapies that are delivered. A number of factors have been found to influence nurses’ provision of sedation therapy in the adult ICU literature, including: lack of standing physician orders, lack of acceptance for sedation protocols (Tanios, de Wit, Epstein, & Devlin, 2009), nurses’ knowledge and attitudes, and perceived autonomy in managing sedative administration (Guttormson, Chlan, Weinert, & Savik, 2010). These findings can reasonably be extrapolated to the population of pediatric critical care nurses. Other literature has shown that nurses’ level of education and clinical experience (Aiken, Clarke, Cheung, Sloane, & Silber, 2003; Coffman et al., 1997; Kutney-Lee, Sloane, & Aiken, 2013) influence their ability to manage patient complications and provide comfort care during acute illness. Less experienced nurses are more likely to administer sedatives, preferring more sedated patients (Egerod, 2002; Guttormson et al., 2010). By contrast, more experienced nurses feel more confident in titrating sedation to patient condition (Walker & Gillen, 2006; Weir & O’Neill, 2008). However, research on workarounds, or behaviors employed by nurses to bypass perceived obstructions in their workflow, has shown that greater seniority and expertise in critical care may make nurses more likely to
deviate from standard protocols that they consider to be unimportant or not useful (Debono et al., 2013). Observed differences in adherence to sedation management protocols across clinician groups (Burns 2012; Ista, de Hoog, Tibboel & van Dijk, 2009; Weir & O’Neill, 2008) suggest that nurses are susceptible to developing professionally cultivated attitudes toward the care of children requiring sedation, which in turn impact their management of patients.

Pediatric critical care nurses function within a team of providers. The teamwork required by PICU care necessitates interaction among multiple providers who may bring varying perspectives and levels of knowledge or skill to the management of pediatric sedation (Schechter, Berde, & Yaster, 2003; E. J. Thomas, Sexton, & Helmreich, 2003). The knowledge base surrounding sedation management is currently divided across numerous fields (Schechter et al., 2003). Research has attempted to ensure consistent communication across disciplines regarding sedation through the use of objective measurement scales, such as the State Behavioral Scale (SBS) (Curley, Harris, Fraser, Johnson, & Arnold, 2006) and the Withdrawal Assessment Tool-version 1 (WAT-1) (Franck et al., 2008; Franck et al., 2012). But these assessment tools have not yet been fully integrated in practice (Larson, Arnup, Clifford, & Evans, 2013) and are not thoroughly embedded in clinical decision-making. This may be because nurses have reported using both their clinical judgment and assessment tools together (Walker & Gillen, 2006) or a result of inconsistent use of these tools among members of the clinical team (Weir & O’Neill, 2008).

Lack of interprofessional collaboration and nurse autonomy (Olmstead, Scott, &
Austin, 2010; Schechter et al., 2003; E. J. Thomas et al., 2003) may complicate the process of providing sedation therapy in the PICU. One survey found that only 55% of nurses felt that nurses and physicians communicated clearly regarding sedation goals (Walker & Gillen, 2006). Nurses attempting to implement sedation protocols may be frustrated by other providers’ lack of adherence (Weir & O’Neill, 2008), which may serve to decrease their apparent or actual protocol compliance. For example, in a recent study of nurses’ satisfaction with using the WAT-1 for patient assessment, 90% of nurses reported that the WAT-1 was a helpful tool in their practice but they also cited a lack of physician willingness to change the patient’s weaning plan on the basis of assessment findings (Suddaby & Josephson, 2013). This reluctance persisted despite reported improvements in communication about sedation and weaning with the implementation of withdrawal assessments.

Nurses caring for children requiring sedation operate within high-volume units, which may struggle with low nurse-to-patient ratios or insufficient staffing, both of which have been shown to increase the risk of iatrogenic patient complications (Carayon & Gürses, 2005; Tubbs-Cooley, Cimiotti, Silber, Sloane, & Aiken, 2013). Specifically with regard to sedation and analgesia management, unit volume and staffing have been found to have a complex relationship with protocol or guideline implementation and adherence: standard protocols may be more likely to be used in larger units (i.e., ≥20 beds), (Tanios, de Wit, Epstein, & Devlin, 2009; Gharavi et al., 2007), but the effect of written guidelines on increasing attention to sedation and analgesia may only last until the point at which high unit volumes and poor staffing serve to decrease compliance (Slomka et al.,
In contrast, the literature on nursing workforce issues has highlighted Magnet-designated hospitals as excellent work environments, with improved nurse and patient outcomes (McHugh et al., 2013). The potential impact of nurse staffing, workloads, and work environments, including the influence of working in a Magnet versus non-Magnet institution on patient outcomes on sedation for mechanical ventilation, remains unexplored.

Achieving an optimal level of sedation – that is, one that makes a child safe and comfortable during the course of their mechanical ventilation using the lowest amount of sedation possible – is a key objective of comfort management in the PICU (Johnson et al., 2012; Playfor et al., 2006). However, adequately sedating critically ill children remains an elusive goal in practice: a recent review of sedation assessments in PICUs around the world found that up to 32% of patients are over-sedated and 11% are under-sedated after pooling observations from a variety of different assessment methods (Vet et al., 2013). Only 58% of children were adequately sedated over the course of the study period. Over-sedation is particularly problematic, as it is associated with numerous clinical problems, including longer duration of mechanical ventilation, extubation failure, and greater cumulative drug exposure (Randolph et al., 2002), which contribute to development of medication tolerance, physical dependence and subsequent iatrogenic withdrawal syndrome (Fonsmark, Rasmussen, & Carl, 1999; Ista et al., 2008). Under-sedation is equally detrimental, as the associated agitation and distress in a confused and disoriented child can result in accidental displacement of intravenous lines or endotracheal tubes (Sorce, 2005) and intolerance of mechanical ventilation (Cheifetz,
2003). Resulting complications can include unplanned endotracheal intubation, airway trauma, hemodynamic instability, and increased lengths of mechanical ventilation and higher mortality (Cheifetz, 2003; Playfor et al., 2006; Vet et al., 2013), not to mention distress for both patients and their parents (Playfor, Thomas, & Choonara, 2000).

Tolerance

Pharmacodynamic tolerance is a purely biochemical phenomenon, characterized by decreased efficacy of a drug over repeat exposures due to cellular adaptation to ongoing receptor binding, such that an increased dose or concentration of a drug is required to produce the same patient response (Barr et al., 2011; Jenkins, 2011). In animal and human models, opioid tolerance is mediated by opioid and N-methyl-D-aspartate (NMDA) receptors in the central nervous system. Normally, opioid-receptor binding causes activation of inhibitory G-proteins and down-regulation of intracellular adenylyl cyclase levels, which are responsible for the clinical effects of analgesia and sedation (Jenkins, 2011; Smith, 2009; Suresh & Anand, 2001). However, following opioid exposure, receptor desensitization leads to a paradoxical hyper-sensitization of this signaling pathway, mediated by down-regulation or internalization of opioid receptors and uncoupling of opioid receptors from inhibitory G-proteins (Suresh & Anand, 2001). Excitatory NMDA receptor interactions contribute to the development of opioid tolerance by increasing intracellular calcium and activating other neural depolarization pathways. The end result of these cell-level changes is hyperalgesia, or increased perception of pain and agitation, rather than the expected opioid-induced analgesia and sedation (Anand et al., 2010; Jenkins, 2011; Suresh & Anand, 2001).
Benzodiazepine tolerance is hypothesized to develop in a similar manner: drug binding to neuronal γ-aminobutyric acid (GABA) receptors leads to inhibitory effects on neurotransmission, but chronic exposure may cause receptor modifications and uncoupling, excitatory glutamnergic neurotransmission, and an increase in NMDA receptors (Allison & Pratt, 2003; Vinkers & Olivier, 2012). The current model suggests that a synergistic combination of most or all of these cellular changes causes benzodiazepine tolerance.

Although the biochemical mechanisms underlying the development of tolerance are common across individuals, there is also variability in the degree of tolerance that patients develop, which may be impacted by factors unique to the individual. For example, in children in particular, age and developmental stage influence the pharmacodynamics of sedation therapy. The CYP2D6 and CYP34A enzymes involved in metabolism of opioids and benzodiazepines may not fully mature until 6 months of age, placing younger children at increased risk for altered responses to these medications (Johnson, Miller, & Hagemann, 2012; Mulla, 2010). Pharmacodynamic idiosyncrasies in the developmentally diverse PICU population present problems for clinicians to use these sedatives effectively and safely.

Other studies have demonstrated racial and ethnic differences in drug metabolism as a consequence of pharmacogenetic variations within populations. Approximately 7% of the white population and up to 30% of the African American population possess alterations in the CYP2D6 enzyme associated with rapid metabolism, placing African Americans at greater risk of experiencing increased drug effects with typical doses
Similarly, up to 34% of African American patients are affected by deficient CYP2D6 enzymes, increasing their risk for adverse drug reactions (Brennan, 2012). Since tests of enzyme functionality are not routinely performed in the clinical setting, age, race and ethnicity may be the only surrogate variables available for understanding their potential mediating or moderating effects on the development of tolerance and physical dependence.

Severity of illness and clinical status are complex variables impacting the metabolism of sedative drugs (Carcillo et al., 2003; Ince et al., 2012), and therefore the quality of sedation management and the duration of exposure to sedatives. Specifically, hepatic and/or renal impairment associated with critical illness may significantly increase the bioavailability of certain drugs, such as morphine (Brennan, 2012; Smith, 2009). Children in the PICU also may experience frequent and rapid changes in clinical status, and the extent to which multiple organ failure or other severe illness states influence sedation therapy and drug tolerance remains to be evaluated thoroughly, though limited research exists (Bergman, Steeves, Burckart, & Thompson, 1991; Dagan, Klein, Bohn, & Koren, 1994; Fonsmark et al., 1999; Hughes et al., 1994; Ince et al., 2012). Similarly, neurologic impairments and/or developmental delays may influence the way in which critically ill children respond to sedative agents, or exhibit behaviors typically managed with sedating medications. Similar to the unique nuances that the organizational context brings to bear on sedation management in the PICU, variability in patient response to analgesic and sedative medications presents a unique challenge in the study of drug tolerance, physical dependence and subsequent iatrogenic withdrawal syndrome.
Weaning and Iatrogenic Withdrawal Syndrome

After recovery from their primary illnesses, children are able to resume responsibility for ventilation and oxygenation, which begins the process of gradual weaning of mechanical ventilation and associated sedation. Discontinuation of mechanical ventilation without adequate sedation weaning can lead to respiratory depression necessitating endotracheal reintubation, which is associated with worse patient outcomes (Cheifetz, 2003). Failure to wean sedative therapy is also problematic, as it is directly related to IWS in physically dependent patients (Cho, O’Connell, Cooney, & Inchiosa, 2007; Darnell, Steiner, Szmuk, & Sheeran, 2010; Ducharme, Carnevale, Clermont, & Shea, 2005; Ista, van Dijk, Gamel, Tibboel, & de Hoog, 2007; Jacobs, Salman, Cotton, Lyons, & Brilli, 2001). IWS is a cluster of physiologic signs and symptoms reflecting autonomic nervous, gastrointestinal and cardiovascular disruptions (e.g., elevated temperature, vomiting, tachycardia). Not only does IWS add to patient discomfort, but also it extends intensive care and hospital lengths-of-stay (Franck, Vilardi, Durand, & Powers, 1998), and creates stress for parents and caregivers (Johnson et al., 2012). The added costs can be considerable.

Assessment and Management of IWS

As pediatric critical care clinicians have come to acknowledge IWS as a complication of PICU care, a large volume of research has been directed towards identifying and assessing its severity. Two instruments were developed concurrently in the United States and the Netherlands, respectively, and tested for use in the PICU: the Withdrawal Assessment Tool-Version 1 (WAT-1) (Franck et al., 2008; Franck et al.,
2012) and the Sophia Observation withdrawal Symptoms-scale (SOS) (Ista et al., 2008; Ista, de Hoog, Tibboel, Duivenvoorden, & van Dijk, 2013). The WAT-1 is an 11-item instrument that consists of four separate assessments performed by the bedside nurse: review of the patient’s medical record for the past 12 hours, direct observation of the patient at rest for 2 minutes, application of progressive stimulus with simultaneous patient assessment, and assessment of post-stimulus recovery time (Appendix 1). The instrument was developed and validated for use in a sample of 83 pediatric patients between 2 weeks to 18 years of age who were recovering from acute respiratory failure and had received greater than 5 days of continuous or around the clock opioid medications (Franck et al., 2008). The WAT-1 screens for symptoms of IWS attributable to either opioid- or benzodiazepine-associated withdrawal, with scores ranging from 0 to 12 points. A cutoff score of ≥ 3 is considered to be indicative of IWS and has high sensitivity and specificity (87% and 88%, respectively; area under the curve 0.94 ± 0.01 [95% confidence interval (CI) 0.93-0.96]) (Franck et al., 2008). In addition to being used as a screening tool for the presence of IWS, peak WAT-1 scores have demonstrated high convergent validity with nurse ratings of withdrawal intensity ($r_s = 0.80$), and were moderately correlated with lengths of opioid and benzodiazepine therapy in the pre-weaning period and length of opioid weaning (Franck et al., 2008), providing further evidence for the instrument’s construct validity. Therefore, peak WAT-1 scores might also be used as an indicator of the severity of IWS symptoms. The Sophia Observation withdrawal Symptoms-scale (SOS) is another tool developed by pediatric experts for evaluating symptoms of IWS in critically ill children.
The SOS demonstrated very good reliability and validity in psychometric testing (83% and 93%, respectively), and a cutoff score of ≥ 4 yielded good sensitivity and specificity for identifying IWS (Ista et al., 2013; Ista, van Dijk, de Hoog, Tibboel, & Duivenvoorden, 2009). The authors suggest that the tool improves upon the WAT-1 by including more signs and symptoms of IWS, such as anxiety, grimacing, and tachycardia (Ista et al., 2008; Ista et al., 2009). However, a direct comparison of the two instruments has never been performed. Neither the WAT-1 nor the SOS is able to distinguish between opioid-related versus benzodiazepine-related IWS, since most pediatric patients receive both for sedation and are typically weaned from both concurrently (Ista et al., 2007). It is important to note that monitoring for IWS is not a standard practice in all institutions.

The treatment of IWS is also an area of significant research interest. Currently, there are no evidence-based guidelines for the treatment of IWS in children; clinicians instead must rely upon their clinical judgment and guidelines for the management of neonatal abstinence syndrome in infants born to substance dependent mothers (American Academy of Pediatrics, 1998; Hudak, Tan, The Committee on Drugs, & The Committee on Fetus and Newborn, 2012). The American Academy of Pediatrics recently released a clinical report recommending that patients be transitioned to longer-acting opioid formulations, followed by 10-20% dose reductions of short-acting opioids every 24 to 48 hours as tolerated until all opioids are discontinued in order to prevent IWS (Galinkin, Koh, The Committee on Drugs, & Section on Anesthesiology and Pain Medicine 2014). Benzodiazepine-related IWS has been treated with long-acting benzodiazepine supplementation, as well as substitution of phenobarbital (J. D. Tobias, 2000). Numerous
studies have evaluated the potential for other sedative medications to prevent (i.e., methadone) or manage the symptoms of IWS: clonidine, dexmedetomidine, and ketamine have all been found to effectively facilitate weaning from opioids and benzodiazepines (Anand et al., 2010; Aydogan et al., 2013; Hünseler et al., 2014; Lugo, MacLaren, Cash, Pribble, & Vernon, 2001; Meyer & Berens, 2001; Tobias, 2006; White & Karsli, 2007). It is important to note that IWS continues to develop in PICU patients despite the implementation of protocols intended to prevent it (Bowens et al., 2011; Ducharme, Carnevale, Clermont, & Shea, 2005; Johnson, Harrison, & Allen, 2010; Meyer & Berens, 2001; Siddappa et al., 2003; Tobias, 2006). For example, few PICUs have integrated weaning protocols into their standards of care (Alexander, Carnevale, & Razack, 2002; Deeter et al., 2011; Ista, de Hoog, Tibboel, & van Dijk, 2009; Jin et al., 2007), and among those that have, protocol compliance remains a challenge (Burns, 2012; Guttormson et al., 2010). Although in a survey of US PICUs, 100% of physicians reported gradually weaning patients from sedative and analgesic drugs, 94% also reported that children experienced IWS symptoms on their units (Twite et al., 2004). This continued incidence of IWS is presumably related to the wide variation in both sedation and weaning protocols, and practice.

Two decades of research has aimed to better characterize IWS and to define its precipitating factors. The two classically identified clinical factors impacting IWS are cumulative dose and duration of sedation. After Finnegan et al. (1975) first identified the phenomenon of withdrawal in neonates born to substance dependent mothers, Arnold et al. (1990) extended the concepts of tolerance and physiologic dependence to a
retrospective study of neonates sedated for extracorporeal membrane oxygenation (ECMO). They found that cumulative doses of fentanyl exceeding 1.5mg/kg and duration of ECMO (and therefore sedation) >5 days were significantly associated with higher odds of IWS (OR = 7.0 and 13.9, respectively). Katz, Kelly and Hsi (1994) subsequently conducted a prospective study of the occurrence of IWS in slightly older critically ill children (aged 1 week to 22 months) receiving mechanical ventilation and continuous infusions of fentanyl. They identified that a threshold cumulative fentanyl dose of 1.6mg/kg and an infusion duration exceeding 9 days were 100% predictive of IWS. Meanwhile, Fonsmark, Rasmussen and Carl (1999) found no associations between IWS and cumulative morphine dose, but total doses of midazolam >60 mg/kg were associated with the incidence of IWS. Until recently, no threshold duration of therapy for benzodiazepines was associated with IWS; however, a retrospective study found that a duration of benzodiazepine therapy exceeding 5 days was predictive (Fernández-Carrión et al., 2013).

Several cutoff doses and durations of therapy have been proposed (Amigoni et al., 2014; Arnold et al., 1990; Dominguez, Lomako, Katz, & Kelly, 2003; Fonsmark et al., 1999; Franck et al., 1998; Katz et al., 1994), but the diversity of patient populations in the PICU and variance in sedation, weaning, and assessment for IWS has resulted in a lack of consensus regarding contributors to IWS. These results strongly suggest that other contextual variables influence a child’s risk for developing IWS. The current biomedical model fails to adequately explain the ongoing incidence of IWS in critically ill children and differential susceptibility between patients. Therefore, the purpose of this dissertation
study was to investigate the development of IWS in critically ill children requiring sedation therapy by exploring variables at the levels of the individual patient, the process and the health care system.

Operational Definitions

Conceptual definitions of tolerance and IWS have been presented in the previous sections. However, for the purposes of the proposed study, a set of operational definitions is needed for key variables of interest that will be referenced throughout the three studies. In particular, standardized instruments were used to assess variables, beginning with the primary outcome of IWS.

As discussed, the WAT-1 (Appendix 1) is an 11-item instrument developed for the purpose of detecting signs and symptoms of clinically significant IWS in children (Franck et al., 2008; Franck et al., 2012). Prior to the start of the RESTORE trial, all clinicians across the 31 participating institutions were trained in the use of WAT-1 scoring and completed a post-test to ensure their comprehension of the material (Curley et al., 2015). After baseline training, each RESTORE nurse co-investigator provided five sets of paired WAT-1 ratings. Scores were evaluated for inter-rater reliability and maintained at greater than 90% throughout the study. Therefore, for the purposes of this dissertation work, WAT-1 scores were used as a valid and reliable indicator of the presence and severity of IWS in study subjects, with the outcome of clinically significant IWS being operationally defined as two or more non-consecutive WAT-1 scores ≥3. In the RESTORE trial, clinically significant withdrawal was defined as the need for rescue therapy (i.e., an opioid or benzodiazepine bolus or increase in opioid or benzodiazepine
infusion) after the start of weaning in order to manage worsening symptoms, which were identified using the WAT-1 (Grant, Scoppettuolo, Wypij, & Curley, 2012). However, due to variations in clinical practice across institutions, not all patients in the RESTORE trial exhibiting signs and symptoms may have received rescue therapy, particularly among control PICUs. In contrast, all sites were required to assess patients using the WAT-1 for symptoms of IWS during sedation weaning, and the threshold score of ≥ 3 has been psychometrically tested (Franck et al., 2008; Franck et al., 2012). Out of concern for potential false positives, the more conservative criterion of two WAT-1 scores ≥3 was used, which has not been previously tested for validity and reliability.

A variety of analgesic and sedative medications are available for use in the PICU (Vet et al., 2013; Zuppa et al., 2005), but this study will focus on the specific contributions of opioids and benzodiazepines to the outcome of IWS. Total sedative exposure was measured by aggregating daily dosing of sedative medications in the RESTORE trial. All opiates were converted to morphine sulfate equivalents, and all benzodiazepines were converted to midazolam equivalents, according to standard conversions: morphine equivalent conversion factors to equal 1mg morphine sulfate were 15µg remifentanil; 15µg fentanyl; 0.15mg hydromorphone; and 0.3mg methadone, and midazolam equivalent conversion factors to equal 1mg midazolam were 0.2mg clonazepam; 0.3mg lorazepam; and 2mg diazepam (Curley et al., 2015).

A limitation of previous investigations is that they did not adequately differentiate between pre- and post-start of weaning medication doses, making previously proposed dose and duration thresholds unusable for prognostic purposes. Therefore, all medication-
related variables in this dissertation study were limited to the preweaning period:
Cumulative doses (in milligrams per kilogram [mg/kg]) were calculated by summing continuous, scheduled and intermittent doses of each agent during the pre-opioid weaning period and dividing by the dosing weight. The mean daily dose was calculated by dividing the cumulative dose by the number of days the specific drug was administered. The peak daily dose was equal to the highest daily dose of each drug administered. Duration of opioid and/or benzodiazepine therapy was recorded based on the total number of days the patient received each agent.

Although it is commonly supposed that children with previous sedative exposures have greater medication needs and thus are more likely to demonstrate tolerance with subsequent exposures, studies have failed to support such an association. Children with a history of opioid exposure do not have higher opioid requirements during or following surgery (Fanning, Stucke, Christensen, Cassidy, & Berens, 2012), and in fact tolerance appeared to occur less frequently among subjects with previous PICU admissions in one study (Anand et al., 2013). Therefore, a history of exposure to opioids and/or benzodiazepines was not examined in either the RESTORE trial or this secondary analysis, and was not expected to significantly impact the results.

Tolerance was recently investigated in a multicenter observational study, in which it was defined as a doubling of the initial (i.e. first 24 hours’) opioid dose over the course of a patient’s hospitalization (Anand et al., 2013). In the absence of clear biomarkers for the development of tolerance, a clinically based definition is the closest available surrogate. For the purposes of this study, the current operational definition of tolerance was adapted to define tolerance as a doubling of the Day 2 opioid dose, with the caveat
that tolerance had to occur before the onset of opioid weaning. This modification was needed to adjust for potential sub-optimal dosing of the initial sedative regimen.

Chapter Aims and Rationales

Chapter 2: Specific Aims.

The purpose of this systematic review of available literature was to identify known or potential risk factors contributing to the prevalence of iatrogenic withdrawal syndrome (IWS) in critically ill children. This paper presents a conceptual model of risk for IWS, which demonstrates the relationships among tolerance, the identified risk factors, and the outcome of clinically significant IWS. Furthermore, the results of this review provide the foundation for the data-based papers to follow. The manuscript was published in the January 2015 issue of Pediatric Critical Care Medicine.†

Rationale.

The conceptual model in this paper was developed through an inductive process of examining the literature and collapsing related risk factors into categories, without any basis in previous theories. However, the classic structure-process-outcome model implemented in healthcare research (Donabedian, 1966) provides a useful framework for understanding the conceptual distinctions made between variables at the process and system levels in this model of IWS risk. To summarize, the structure of a healthcare organization consists of characteristics that indirectly influence patient outcomes by

†The manuscript in Chapter 2 is the author’s original work and the copyright is as follows: Pediatric Critical Care Medicine: 1 January 2015 – Volume 16 – Issue 2 – p 175–183, Wolters Kluwer Health Lippincott Williams & Wilkins©. While the manuscript is reproduced free of charge, no modifications are permitted without the permission of the copyright holder.
shaping the environment of care delivery. Typically these features remain stable over time, and include factors such as hospital size and staff professionalization (Hearld, Alexander, Fraser, & Jiang, 2008). In contrast, processes are care activities performed by individuals within the organization, which are by their nature dynamic and changing over time. The benefit of simultaneously considering patient-, process- and system-level factors together is the ability to identify potential interactions between process and systems variables that contribute to patient outcomes (Hearld et al., 2008), while adjusting for differences in patient populations across healthcare institutions.

Chapter 3: Specific Aims.

The purpose of this paper was to use data from baseline pre-randomization subjects in the RESTORE trial to further evaluate the relationships among tolerance, weaning, and IWS. Specifically, patterns of opioid and benzodiazepine weaning as they occurred in PICUs across the United States in typical practice settings was assessed and characterized. The information obtained about the effects of sedative dose, duration, and other clinical factors on tolerance and subsequent patterns of weaning provide key information for the construction of a predictive model in the final paper. This manuscript has been submitted for review for publication.

Rationale.

The pre-randomization RESTORE subjects provided a unique cohort for exploring the relationships of interest in this study, since similar data were collected as in the larger trial and subjects were assessed for pain, agitation, sedation and IWS using validated assessment instruments. Therefore, unlike other observational studies that may rely on
clinicians’ subjective assessments of these patient states or retrospective chart reviews, this dataset contained rigorously measured data points that reflected usual practice at each institution. Some of the participating PICUs had standardized sedation assessment processes already in place, but they were not necessarily being used to titrate or wean sedative therapy. These circumstances offered a view of usual practice prior to implementation of a standardized, goal-directed protocol. This dataset also provided a test group for developing a standard approach to defining start of opioid weaning, tolerance, and weaning patterns in a smaller, more manageable patient cohort.

Chapter 4: Specific Aims.

The purpose of this paper was to build upon the findings of the previous two investigations, in order to construct a predictive model of IWS risk using data from subjects in the RESTORE trial. The resulting model could be used as the foundation for a risk assessment tool that would help guide weaning and other preventive strategies in the clinical setting. This manuscript has been submitted for review for publication.

Rationale.

Up to this point, there have been a few attempts to identify risk factors for IWS (Amigoni et al., 2014; Dominguez et al., 2006; Dominguez et al., 2003; Fernández-Carrión et al., 2013; Ista et al., 2013), which have met with varying degrees of success. Key limitations of these previous approaches have been: sampling from a single center, use of small study samples, and failure to distinguish between preweaning medication doses. Results of these analyses have been inconsistent, even with respect to the most widely reported risk factors of sedative dose and duration (Amigoni et al., 2014;
Dominguez et al., 2003; Fernández-Carrión et al., 2013). In addition, older studies have been hampered by a lack of standardized assessment instruments for IWS (Birchley, 2009).

The convergence of a number of factors therefore supports the development of a new predictive model of IWS in this study. First, the recently completed RESTORE trial was the largest study of sedation management ever conducted in pediatric critical care, and the dataset was designed with the objective of evaluating IWS as a secondary outcome. Routine screening for IWS was performed using the WAT-1, a well-validated instrument that is being used in an increasing number of studies of IWS (Amigoni et al., 2014; Fisher, Grap, Younger, Ameringer, & Elswick, 2013; Jeffries, McGloin, Pitfield, & Carr, 2012). Finally, the trial was multi-center, which provided the opportunity to examine the influence of a diverse group of providers and health systems on the outcome of interest, an area that has previously been underexplored in the literature.

Strengths and Limitations

This dissertation had the benefit of using data from the largest clinical trial of sedation management ever conducted in pediatric critical care for secondary analysis. The research question of the RESTORE trial – whether pediatric patients with acute respiratory failure managed per a nurse-led, goal-directed sedation management protocol experienced fewer days of mechanical ventilation – was directly related to the outcomes of interest in the analyses to follow. Not only were relevant data points collected using the stringent site auditing, data monitoring and quality control processes of a large clinical trial, but the incidence of IWS was also a secondary outcome measure of the
RESTORE trial. Thus, it was both feasible and justifiable to conduct a secondary analysis of this existing data set to address the specific aims of this dissertation.

However, because two of the three studies were secondary analyses, the findings are limited by any weaknesses of the parent study. Although highly unlikely, site randomization of the RESTORE trial may have failed to yield a representative sample of critically ill children in the PICU, impacting generalizability of the results. Undetectable differences between the control and intervention sites may have occurred, potentially confounding the effect of the nurse-led, goal-directed intervention. Finally, this dissertation included process- and system-level variables in its analyses, based on an untested conceptual framework. Since clinical sites reported their data in aggregate, the influence of systems factors could not be linked to individual patients. Therefore, any conclusions drawn by this study regarding the contributions of system-level variables to the development of IWS will require prospective validation in future studies. Since prospective data collection did not take place for these dissertation analyses, both the approach and findings are limited to the data collected during the course of the RESTORE trial.

Significance

The variables driving the development of IWS, beyond the biologic and pharmacologic level, are presently uncharacterized and pose a critical barrier to progress in IWS science. This study provides valuable evidence and context for understanding the phenomenon of IWS within the unique clinical circumstances in which it occurs. The results of these three studies will advance our current approach to management of
symptoms of IWS in the PICU. In particular, prospective validation of the predictive model of IWS risk contributed by this study is a logical next step towards a robust program of research, and further studies would harness these empirically demonstrated risk factors to support future projects, for example identifying biomarker changes associated with IWS in critically ill children.
CHAPTER 2
SYSTEMATIC REVIEW AND CONCEPTUAL MODEL

Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: A systematic review and conceptual model

Kaitlin M. Best, RN, MS
Joseph I. Boullata, PharmD, RPh, BCNSP
Martha A. Q. Curley, RN, PhD, FAAN

1PhD Student
School of Nursing
University of Pennsylvania
Claire M. Fagin Hall
418 Curie Boulevard - #425
Philadelphia, PA 19104-4217 USA

2Professor of Pharmacology and Therapeutics
School of Nursing
University of Pennsylvania

3Ellen and Robert Kapito Professor in Nursing Science
School of Nursing
Anesthesia and Critical Care Medicine
University of Pennsylvania

Corresponding Author: Kaitlin Best
Available at: kbest@nursing.upenn.edu

Financial support: University of Pennsylvania Hillman Scholar’s Program in Nursing Innovation
Key words: Sedation, analgesia, dependence, tolerance, iatrogenic withdrawal syndrome, WAT-1, pediatric intensive care unit
Abstract

Objective: Analgesia and sedation are common therapies in pediatric critical care, and rapid titration of these medications is associated with iatrogenic withdrawal syndrome (IWS). We performed a systematic review of the literature to identify all common and salient risk factors associated with IWS and build a conceptual model of IWS risk in critically ill pediatric patients.

Data sources: Multiple databases, including PubMed/Medline, EMBASE, CINAHL, and the Cochrane Central Registry of Clinical Trials were searched using relevant terms from January 1, 1980 to August 1, 2014.

Study selection: Articles were included if they were published in English and discussed IWS following either opioid or benzodiazepine therapy in children in acute or intensive care settings. Articles were excluded if subjects were neonates born to opioid- or benzodiazepine-dependent mothers, children diagnosed as substance abusers, or subjects with cancer-related pain; if data about opioid or benzodiazepine treatment were not specified; or if primary data were not reported.

Data extraction and synthesis: In total 1395 papers were evaluated, 34 of which met the inclusion criteria. Most papers were prospective observational or interventional studies. To facilitate analysis, all opioid and/or benzodiazepine doses were converted to morphine or midazolam equivalents, respectively. A table of evidence was developed for qualitative analysis of common themes, providing a framework for the construction of a conceptual model.
**Findings:** The strongest risk factors associated with IWS include duration of therapy and cumulative dose. Additionally, evidence exists linking patient, process and system factors in the development of IWS.

**Conclusions:** Given the state of existing evidence, well-designed prospective studies are required to better characterize IWS in critically ill pediatric patients. This review provides data to support the construction of a conceptual model of IWS risk that, if supported, could be useful in guiding future research.
Introduction

Sedation is commonly used in pediatric intensive care to reduce the physiologic and psychological stress associated with critical illness. However, it is known that rapid weaning or abrupt cessation of sedation therapy in drug tolerant children precipitates iatrogenic withdrawal syndrome (IWS)\textsuperscript{1} – a cluster of symptoms that can have deleterious effects on patient recovery and hospitalization.\textsuperscript{2–4}

The prevailing mechanistic theory of drug tolerance involves receptor desensitization and up-regulation of excitatory intracellular pathways.\textsuperscript{5–7} Anand et al. provide a comprehensive review of physiologic mechanisms in pharmacodynamic tolerance.\textsuperscript{2} Clinically, tolerance manifests as a need for increased medication to achieve consistent therapeutic effects. Tolerance, escalating doses, and prolonged treatment are coupled with the development of physiologic dependence. Once patients manifest tolerance and dependence, termination of therapy without measured weaning precipitates IWS.\textsuperscript{3}

Most studies on opioid and benzodiazepine IWS have focused on characterizing symptoms in the pediatric population, developing screening and assessment tools, or testing treatment regimens. A fundamental question in understanding IWS has been overlooked: what specific factors predispose pediatric intensive care unit (PICU) patients to developing IWS? Knowledge of IWS risk factors and their inter-relationships may help clinicians prevent IWS. We performed a systematic review of the literature to identify all common and salient risk factors associated with IWS, with the intention of building a conceptual model of IWS that will guide future research.
Methods

PubMed/Medline, EMBASE, CINAHL, and the Cochrane Central Registry of Clinical Trials were searched for original research on opioid- and/or benzodiazepine-related IWS in critically ill children. Given the limited number of studies in this area, time limits were set between January 1, 1980 and August 1, 2014. Corresponding exploded MeSH or EMTREE terms were used when possible (Table 2-1).

Articles published in English and discussing IWS following either opioid or benzodiazepine therapy in children in intensive care settings were included. Age limits were set from 2 weeks post-gestation to 18 years. Articles were excluded if data about opioid or benzodiazepine treatment were not specified; if primary data were not reported; or if subjects were neonates born to opioid- or benzodiazepine-dependent mothers, children diagnosed as substance abusers, or subjects with cancer-related pain. Relevant reviews were referenced to capture key studies missed by the search criteria, using ancestry searching.

Study data were extracted into tables of evidence and qualitatively synthesized. Examined data points included study population, location, sample size, sedative medications and mode of administration, IWS assessment method, weaning method, and number and percentage of IWS subjects. For cross-study comparisons, opioid and benzodiazepine doses were converted to morphine and midazolam equivalents. Specifically, morphine equivalent conversion factors to equal 1mg morphine sulfate were as follows: 15µg remifentanil; 15µg fentanyl; 0.15mg hydromorphone; and 0.3mg methadone. Midazolam equivalent conversion factors to equal 1mg midazolam were:
0.2mg clonazepam; 0.3mg lorazepam; and 2mg diazepam. Qualitative analysis of the retrieved articles’ results was used to identify both common and novel factors and construct categories of risk. The authors then used an iterative consensus process to develop a conceptual model describing IWS risk that was organized to include patient, process, or system factors contributing to IWS in pediatric patients.

PRISMA guidelines were followed in the conduct and reporting of this study, including consultation with a research librarian in designing the search strategy. Selected studies were evaluated for quality using a criteria-based assessment method for randomized controlled trials (adequacy of randomization and blinding, presence of allocation concealment, and intention-to-treat analysis) and the Newcastle-Ottawa Quality Assessment Scale for observational studies. Randomized controlled trials were rated high, medium and low quality, with a single category deduction for each missing criterion. The Newcastle-Ottawa Quality Assessment Scale assigns star ratings for important elements of observational study design, with a maximum possible score of nine stars. Studies were rated high (7-9 stars), medium (4-6 stars) or low quality (1-3 stars) based on the total number of stars received.

Results

As outlined in Figure 2-1, 34 data-based articles met inclusion criteria for this review. Twenty-three studies reported combination opioid and benzodiazepine therapy (Table 2-2), while 9 reported opioid-only therapy (Table 2-3), and two reported benzodiazepine-only therapy (Table 2-4) (Supplemental Digital Content).
The majority of articles (74%) included <50 subjects. The incidence of either opioid- or benzodiazepine-related IWS (Figure 2-2) was widely variable; for example, frequency of IWS symptoms attributable to cessation of either opioids or benzodiazepines in studies of concurrent therapy ranged from 5%/12 to 87%13.

Common themes suggested three categories of risk factors associated with IWS: patient-, process-, and system-level factors, which were synthesized into a conceptual model (Figure 2-3) that organizes the presentation of evidence in this review. The majority of studies investigated patient-level variables, including age, criticality, duration of therapy and cumulative dose. Process-level factors were directly related to the approach of providing sedation, and included the use of sedation and/or IWS assessment tools and protocols. System-level factors were infrequently cited, but reflected structural variables that influence clinician practice within the healthcare system, such as interprofessional collaboration and protocol compliance. Each will be presented in the following sections.

Patient-Level Factors

Age. Moderate quality evidence supports a relationship between age and IWS.14-20 Prospective studies have shown that cumulative opioid dose is related to age,16 and that younger patients experience higher incidences of IWS.18 Similarly, among retrospective studies assessing the abrupt cessation of continuous fentanyl15 or midazolam infusions,19 younger age was associated with neurologic symptoms of IWS, such as irritability/agitation and seizures.

Older age was also associated with IWS in children.17 For example, subjects with the highest daily doses (morphine >60 µg/kg/hr or midazolam >250 µg/kg/hr) tended to
be older (median 6 years vs. 1.4; \( p = 0.0017 \)) even when doses were adjusted for weight. \(^{20}\) These subjects also had a greater incidence of IWS: 40% of older subjects versus 12% of other subjects (\( p \leq 0.001 \)).

Criticality. Limited data from moderate quality studies suggests that severity of illness, particularly involving brain injury or ischemia, contributes to a higher incidence of IWS. \(^{19,24}\) Low serum albumin concentration in infants receiving midazolam in one retrospective study was associated with IWS-related neurologic disturbances. \(^{19}\) Several studies noted that children with pre-existing seizure disorders or hypoxemic brain injuries are more likely to experience IWS. \(^{20,23}\)

Duration of therapy. Many studies of varying quality related duration of opioid and/or benzodiazepine therapy to the incidence of IWS. \(^{1,4,8,16,17,25,33,34,35}\) Subjects with longer PICU or hospital lengths of stay, \(^{8,29}\) more ventilator days, \(^{8,29}\) and longer ECMO therapy \(^{4,28}\) were more likely to experience IWS. In one paper, subjects in a randomized trial of methadone-facilitated weaning were more likely to experience treatment failure with longer PICU lengths of stay, particularly after receiving fentanyl for \( \geq 9 \) days. \(^{29}\) In two small studies, subjects experiencing IWS received at least 10 days of opioid or benzodiazepine therapy. \(^{34,35}\)

The majority of studies in this category directly evaluated relationships between length of opioid and/or benzodiazepine therapy and IWS. \(^{1,8,16,17,25,27,30,33,36}\) Some used statistical methods to establish predictive opioid thresholds, with cut-off lengths of therapy ranging from \( \geq 5 \) \(^{27}\) to 8 days (OR=18, \( p = 0.02 \)). \(^{25}\) Exposures longer than 9 days were 100% predictive of IWS. \(^{27}\) The remaining studies evaluated correlations between length of opioid infusion and IWS outcome or score, \(^{1,16,26,32}\) which ranged from
moderately \((r=0.20, p=0.02)\)\(^1\) to strongly positive \((r=0.70, p<0.05)\).\(^{26}\) Among prospective studies investigating the duration of opioid therapy and IWS, all exceeded the 5-day threshold proposed in previous research (Figure 2-4).\(^{1,8,12,16,17,25-27,30}\)

No widely accepted threshold duration of therapy for benzodiazepines currently exists, although a recent retrospective study found that a duration of benzodiazepine therapy exceeding 5 days had 83% sensitivity and 92% specificity for predicting IWS.\(^{36}\) Positive correlations between duration of benzodiazepine therapy and IWS have been identified in other studies of concurrent opioid and benzodiazepine administration.\(^{1,8,17,30,31}\) Similar to opioid duration, these correlations are moderate, ranging from \(r=0.23\) \((p<0.01)\)\(^8\) to \(r=0.52\) \((p<0.001)\).\(^{30}\) In several prospective studies, subjects with IWS received benzodiazepine therapy in excess of 10 days (Figure 2-5).\(^{12,21,30,37}\)

Dose. Strong reproducible evidence exists for a relationship between opioid and/or benzodiazepine dose and IWS.\(^{1,4,8,12-14,16,17,20,21,23-30,32,35,36,38-40}\) Description of dosing varied, with the most common measure being cumulative dose (total amount of drug administered during treatment).

Several studies focused on the association between prescribed opioid dose and IWS risk.\(^{4,16,24-28,36,38}\) Whereas one study found that a cumulative morphine equivalent dose of >106.7mg/kg was associated with 7-fold higher odds of IWS,\(^{28}\) another identified that a threshold cumulative dose of ≥166.7mg/kg (morphine equivalents) was 100% predictive of IWS.\(^{27}\) Lower thresholds have also been proposed in unique patient populations, for example, >80mg/kg doses after ECMO support \((OR=13.0, p=0.003)\).\(^4\) This threshold had 85% sensitivity and 70% specificity for predicting IWS. A more
recent retrospective study found that 32 mg/kg morphine equivalent doses had 83% sensitivity and 85% specificity for predicting IWS in children who received mean cumulative doses of midazolam above published averages.\textsuperscript{36}

Only one study of benzodiazepine-associated IWS compared cumulative dose with the incidence of withdrawal,\textsuperscript{14} finding that an infusion rate greater than 0.3mg/kg/h (midazolam equivalents) resulted in symptoms consistent with IWS. Cumulative dosages in midazolam equivalents ranged from 0.9mg/kg to 25.3mg/kg,\textsuperscript{14} but statistical analyses were not performed. However, in a study of mixed opioid and benzodiazepine administration, a cumulative benzodiazepine dose threshold of >60mg/kg (midazolam equivalents) was significant ($p<0.05$).\textsuperscript{23}

Many studies evaluating IWS symptoms attributable to either opioids or benzodiazepines reported dosage associations:\textsuperscript{1,8,12,13,17,20,21,23,29–31,34,35,39} one found moderate correlations with opioid dose alone,\textsuperscript{31} and four with both opioid and benzodiazepine dose.\textsuperscript{1,13,30,36} The remaining studies reported differences between groups with and without IWS in cumulative opioid and/or benzodiazepine doses,\textsuperscript{8,12,17,23,29,39} or had too few subjects for statistical analysis.\textsuperscript{21,34,35} The prospective studies were graphically compared with the dose thresholds proposed for opioids (Figure 2-6) and benzodiazepines (Figure 2-7), respectively. This analysis showed that many studies reported mean or median doses well below the proposed thresholds among subjects with IWS.\textsuperscript{1,12–14,17,21,30}

### Process-Level Factors

**Sedation protocol.** Although several authors have noted the importance of standardized sedation protocols in reducing the incidence of IWS,\textsuperscript{12,40} little high-quality
Evidence exists to directly illustrate the proposed relationship. Three studies cited the lack of a sedation management protocol as a risk factor for the development of IWS, and two moderate-quality studies showed reductions in IWS rates in the intervention groups when sedation protocols were implemented.

Drug choice. Some evidence supports an association between drug choice and IWS. Specifically, four studies observed an association between fentanyl and IWS symptoms in children. Rates of IWS are lower in subjects receiving morphine rather than fentanyl infusions (9% v. 57%; \(p=0.01\)). In a retrospective chart review of subjects who developed a “movement disorder” following discontinuation of infusions, fentanyl was the only medication common to all subjects (\(p<0.001\)).

Methadone has been evaluated in several studies as a potential weaning agent to prevent IWS symptoms in drug-tolerant pediatric patients. However, one study determined that the greatest risk factor for IWS among subjects receiving prophylactic methadone was inadequate methadone dosing. Multi-drug sedation therapy has also been proposed as an additional risk factor for IWS.

Mode of administration. Low to moderate quality articles reported more frequent IWS among subjects receiving continuous infusions of opioids and/or benzodiazepines. Although authors noted that continuous infusions could theoretically contribute to faster development of drug tolerance, none of the studies in this review specifically compared the effects of intermittent versus continuous administration on the incidence of IWS.

Weaning. Fewer than half of the cited studies (43%) utilized a standardized weaning protocol, and even with a standard protocol, withdrawal
rates ranged from 5%\(^1\text{2,34}\) to 87%\(^1\text{3}\). In the remaining studies, opioids, benzodiazepines, or both were either abruptly discontinued\(^1\text{9,23,24,35}\) or weaned on a variable basis.\(^1\text{8,14–17,20,26,28,31,39–41}\) Weaning patterns differed substantially: in one prospective study, opioid dose changes in the first 24 hours of weaning ranged from −24mg/kg to +14mg/kg (morphine equivalents).\(^1\text{6}\) Two studies reported that use of a weaning protocol could reduce the incidence of IWS.\(^1\text{16,38}\) Some studies abruptly discontinued sedative therapy due to the substitution of other agents, such as clonidine,\(^1\text{16,20,41}\) dexmedetomidine,\(^1\text{16,39}\) methadone,\(^1\text{17,21,33,34,38,41}\) or ketamine.\(^41\) Despite prophylactic therapy, IWS still occurred in 5\%\(^3\text{4}\) to 33\%\(^3\text{3}\) of subjects.

Sedation/withdrawal assessment. Although many studies of IWS have focused on instrument development,\(^1\text{1,8,13,17,30}\) few studies have evaluated the influence of routine sedation assessment on the incidence of IWS. Some authors have commented on the issues of over-sedation and development of tolerance,\(^1\text{16,38,40,42}\) but no studies have specifically evaluated relationships among adequate sedation, standardized assessment, and IWS.

System-Level Factors

Weaning sedation requires a time-sensitive titration plan that may not be able to be accomplished in the PICU when intensive care beds are limited. In addition, local hospital-based policies may not allow for the use of some sedatives agents outside the PICU. No paper cited in this review evaluated the impact of PICU census, bed availability, or local policies regarding the use of sedatives in non-ICU areas on the incidence of IWS.
Management of critically ill children also necessitates an interprofessional team approach. Disagreements within the care team regarding optimal sedation can lead to inconsistencies in sedation practices that may predispose children to IWS. Failure of interprofessional collaboration, along with variability in training and experience with sedation management may influence compliance. Poor sedation or weaning protocol compliance has been shown to increase the incidence of IWS.

Discussion

To date, the strongest risk factors associated with IWS include duration of therapy and cumulative dose. Less evidence exists for relationships with age, criticality, sedation/weaning protocols, and sedation/IWS assessment. This review found few prospective studies offering data specific to opioid- and/or benzodiazepine-related IWS risk factors. It was often necessary to search for any mention of associated risk and extrapolate risk from reported relationships with other variables. The proposed conceptual model (Figure 2-3) illustrates how the convergence of patient- and process-level factors within a system context may contribute to IWS.

Studies linking the duration of opioid therapy and IWS proposed that a threshold of \( \geq 5 \) days\(^{25,27} \) was predictive of IWS (Figure 2-4). Duration of therapy as a risk factor for benzodiazepine-related IWS has not been demonstrated, although a 10-day duration\(^{30} \) seems contributory (Figure 2-5). Authors found relationships between cumulative dose of opioid and/or benzodiazepine and duration of infusion,\(^{13,32,34} \) and cumulative benzodiazepine doses as risk factors,\(^{23} \) albeit from studies with small sample sizes and inconsistent results. The observed relationship between dose and duration may be too
interdependent to determine individual contributions to IWS. For example, a recent study found that the primary outcome of doubling of daily medication dose (tolerance) was more likely to occur with infusions lasting >7 days.\textsuperscript{43}

Several studies\textsuperscript{4,15,25,26} in this review reported IWS accompanying opioid doses below proposed thresholds, which is potentially attributable to patient-level variability (e.g., pharmacogenetics, body composition, criticality). Similarly, cumulative dose as a risk factor for benzodiazepine-related IWS is not adequately supported in the current literature, as IWS was seen in subjects receiving less than the proposed threshold. Other factors such as criticality may obscure the relationships among dose, duration and IWS. Physiologically, as illustrated in the conceptual model, a patient’s therapeutic regimen – medication doses, duration of therapy, and mode of administration – may all act synergistically in contributing to the development of tolerance.

Age, size, and dosing weight are interrelated, so the observation that older children tend to receive higher doses of opioids and benzodiazepines\textsuperscript{20} is not surprising. Furthermore, drug metabolism and excretion, and behavioral responses to discomfort, are related to a child’s development.\textsuperscript{44} Studies in this review included different age ranges, further complicating this picture. More studies with adequate representation of all age groups are required to demonstrate a more definitive relationship with IWS risk.

Inconsistencies in weaning protocols complicate the analysis of IWS risk, since abrupt cessation or rapid weaning has been shown to precipitate withdrawal symptoms.\textsuperscript{2,8,29,42,45} The lower incidence of IWS in studies with specified weaning protocols\textsuperscript{12,29,30,37} may be an indication of the importance of a weaning plan on IWS risk. Conversely, the fact that IWS occurred in controlled, prospective studies with
standardized weaning protocols\textsuperscript{21,33,34} suggests that protocol compliance or failure leading to IWS must be addressed.

Among opioids, fentanyl has a greater potential for inducing tolerance due to its shorter half-life and greater opioid receptor affinity.\textsuperscript{2} More articles in this review reported IWS in subjects receiving fentanyl than with any other opioid.\textsuperscript{4,13,15,41} In addition, most of the studies that reported IWS in patients receiving continuous infusions also administered fentanyl,\textsuperscript{4,15,19,34,39,40} which could be the mechanism driving the proposed relationship between mode of administration and IWS. However, given the prevalence of fentanyl use, higher administered doses of both opioids and benzodiazepines before the start of weaning, and longer durations of therapy,\textsuperscript{1,8} other confounding factors may have influenced the outcome of IWS.\textsuperscript{13} This review presents evidence indicating that fentanyl is more likely to cause IWS than other opioids, but more research is necessary.

Only half of the studies used validated instruments to assess subjects’ IWS.\textsuperscript{1,4,8,12,13,16,17,21,22,25–30,38,39} Finnegan’s Neonatal Abstinence Score (NAS) tool has not been validated outside of the neonatal population,\textsuperscript{46} despite its use in a quarter of the studies in this review. Establishing the validity and generalizability of other IWS assessment instruments is challenging, and studies applying validated IWS assessment tools (e.g. WAT-1,\textsuperscript{1,8} SOS\textsuperscript{17,47}) are needed. IWS will remain difficult to quantify objectively until biological markers are available.

Analysis of the literature reveals an evolving discussion of IWS risk in terms of tolerance- and non-tolerance-related factors. Drug choice, duration of therapy, mode of administration, and cumulative dose may be substitute measures for tolerance. Age and criticality are patient-level variables that may constitute risks for IWS independent of
tolerance. Process-level variables related to clinician decision making, which may be driven by policies of the larger healthcare system, also contribute to IWS risk but not tolerance. However, system-level factors have not been consistently recognized or explored in the existing literature. For example, there is consensus that weaning sedation requires a time-sensitive titration plan that may not be able to be accomplished in the PICU when intensive care beds are limited. Providers may need to move patients out of the PICU as soon as their primary condition has stabilized. In addition, local policies may not allow the use of some sedatives agents in non-ICU areas, further limiting providers’ ability to maintain a consistent weaning plan in some children. However, none of these factors were addressed in the articles assembled in this review. Further research is needed to examine the effect of system-level factors on patients’ risk for developing IWS.

This study has important limitations. Small sample sizes were problematic for achieving requisite statistical power in several included studies, and the overall quality of the available data was moderate. In addition, due to the authors’ limitations, articles published in languages other than English could not be included in this review. This review was performed according to the PRISMA statement, where applicable, although an assessment of the risk of bias for each study was not performed. A registered protocol also was not used in the conduct of this review. A meta-analysis of the selected studies could not be completed, due to low levels of evidence and significant heterogeneity in the populations of the included studies.

Conclusion

This is the first systematic review of risk factors associated with IWS in the critically ill pediatric population that identifies risk factors at the level of the patient,
process, and system, and describes their relationship with the development of tolerance to opioids and benzodiazepines. Of all the factors identified, duration of therapy and cumulative dose are the most predictive of IWS, as has been suggested by other authors. However, this review particularly highlights the need to further explore process and system variables, such as sedation/IWS assessment, and protocol adherence. There are many remaining questions for future studies on risk factors associated with IWS. This model can be used to guide the design and reporting of future studies on IWS in critically ill children.
Acknowledgements

We would like to thank the Hillman Foundation for providing support for the doctoral education of K. M. B. as a Hillman Scholar in Nursing Innovation, which included the time spent in developing this manuscript.
Works Cited


46


Figures and Tables

Figure 2-1. Systematic search and selection process

- Records identified through database searching (n = 1518)
- Additional records identified through other sources (n = 1)
- Records after duplicates removed (n = 1395)
- Records excluded (n = 1190)
  - Reviews or editorials
  - Animal/in vitro studies
  - Adult studies
  - Substance abuse studies
  - Studies of neonates born to substance-dependent mothers
  - No full-text available
- Records screened (n = 205)
- Full-text articles assessed for eligibility (n = 114)
- Full-text articles excluded (n = 91)
  - Adult studies
  - Studies of neonates born to substance-dependent mothers
  - No data on sedation regimen
  - Full-text article not available in English
- Studies included in qualitative synthesis (n = 33)
Figure 2-2. Proportion of subjects with IWS relative to the total number of subjects among included studies

Note: Mixed includes studies where the subjects received both opioids and benzodiazepines.
Figure 2-3. Risk for Iatrogenic Withdrawal Syndrome (IWS). Conceptual model relating three levels of risk factors for IWS in critically ill children.
Figure 2-4. Cross-study comparison of duration of opioid therapy in opioid-only and mixed agent (i.e. opioid and benzodiazepine administration) studies, among subjects with IWS

**Duration of Opioid Therapy Among Subjects with IWS**

- **Katz et al., 1994**
- **French & Nocera, 1994**
- **Dominguez et al., 2003**
- **Fisher et al., 2013**
- **Jin et al., 2007**
- **Ista et al., 2008**
- **Franck et al., 2008**
- **Franck et al., 2012**
- **Ista et al., 2013**

Reference for 5 day threshold: Katz, Kelly, & Hsi (1994)²⁷
Note: Bars represent mean ± SD, median and IQR, or median and min-max, as data were reported in the original studies; the size of each square corresponds to the size of the study sample, with increasing size for larger samples.
Figure 2-5. Cross-study comparison of duration of benzodiazepine therapy among subjects with IWS

Duration of Benzodiazepine Therapy Among Subjects with IWS

* Duration includes medication taper; ** Reported duration only applies to 9 patients receiving lorazepam; *** Authors did not specify medication for the listed duration of sedation. Reference for 10 day threshold: Ista, et al. (2008)

Note: Bars represent mean ± SD, median and IQR, or median and min-max, as data were reported in the original studies; the size of each square corresponds to the size of the study sample, with increasing size for larger samples.
Figure 2-6. Cross-study comparison of cumulative dose of opioids among subjects with IWS

**Opioid Dose Ranges Among Subjects with IWS**

- Katz et al., 1994
- French & Noore, 1994
- Franck et al., 1998
- Dominguez et al., 2003
- Fisher et al., 2013
- Meyer & Berens, 2001*
- Franck et al., 2004*
- Jin et al., 2007
- Franck et al., 2008*
- Isla et al., 2008*
- Franck et al., 2012
- Bowens et al., 2011*
- Isla et al., 2013**

* Provided dose range for total study group, not IWS subjects specifically; ** Values not calculated in original study.

Reference for 106.7 mg/kg (morphine equivalents) threshold: Arnold, Truog, & Orav (1994)²⁸

Note: Bars represent mean ± SD, median and IQR, or median and min-max, as data were reported in the original studies; the size of each square corresponds to the size of the study sample, with increasing size for larger samples.
Figure 2-7. Cross-study comparison of cumulative dose of benzodiazepines among subjects with IWS

**Benzodiazepine Dose Ranges Among Subjects with IWS**

- Hughes et al., 1994*
- Franck et al., 2004**
- Jin et al., 2007
- Ista et al., 2008**
- Franck et al., 2012
- Ista et al., 2013

*Values not calculated in original study; **Provided dose range for total study group, not IWS subjects specifically.

Reference for 60 mg/kg (midazolam equivalents) threshold: Fonsmark, Rasmussen, & Carl (1999)\(^{23}\)

Note: Bars represent mean ± SD, median and IQR, or median and min-max, as data were reported in the original studies; the size of each square corresponds to the size of the study sample, with increasing size for larger samples.
Table 2-1. Detailed search strategy

Medline/PubMed AND CINAHL search strategy for pediatric studies

<table>
<thead>
<tr>
<th>Search</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>ventilator* OR ventilation* OR respirator* OR &quot;Respiration, artificial&quot;[Mesh] OR &quot;artificial respiration&quot;</td>
</tr>
<tr>
<td>#2</td>
<td>weaning OR weaned OR weans OR wean OR discontinue OR terminat*</td>
</tr>
<tr>
<td>#3</td>
<td>hypnotic* OR depressant* OR sedat* OR opioid* OR narcotic* OR benzodiazepine* OR fentanyl OR morphine* OR diazepam OR lorazepam OR midazolam</td>
</tr>
<tr>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

Filters: English; Child: birth (manual exclusion of < 2 weeks)-18 years

EMBASE search strategy for pediatric studies

<table>
<thead>
<tr>
<th>Search</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>“ventilator” OR “ventilation” OR “respirator” OR &quot;artificial respiration&quot; OR artificial ventilation/exp OR assisted ventilation/exp</td>
</tr>
<tr>
<td>#2</td>
<td>“weaning” OR “weaned” OR “weans” OR “wean” OR “discontinue” OR “terminate” OR “termination” [NOTE: No EMTREE term for ventilator weaning]</td>
</tr>
<tr>
<td>#3</td>
<td>“hypnotic” OR “depressant” OR “sedative” OR hypnotic sedative agent/exp OR “opioid” OR “narcotic” OR opiate/exp OR narcotic agent/exp OR “benzodiazepine” OR benzodiazepine/exp OR fentanyl OR morphine OR diazepam OR lorazepam OR midazolam</td>
</tr>
<tr>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

Limits: English; Child: birth (manual exclusion of < 2 weeks)-18 years
Table 2-2. Articles on concurrent opioid and benzodiazepine therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Sample Size</th>
<th>Medications</th>
<th>Mode of Administration</th>
<th>IWS Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Control Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowens et al. (2011)³⁹</td>
<td>PICU (US)</td>
<td>N = 78</td>
<td>Fentanyl, midazolam</td>
<td>Continuous</td>
<td>MNWS</td>
</tr>
<tr>
<td><strong>Prospective Interventional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin et al. (2007)¹²</td>
<td>PICU (Korea)</td>
<td>N = 53</td>
<td>Fentanyl, midazolam</td>
<td>Bolus, continuous</td>
<td>Modified NAS, physiologic s/sx</td>
</tr>
<tr>
<td><strong>Prospective Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ista et al. (2013)¹⁷</td>
<td>PICU (Netherlands)</td>
<td>N = 154</td>
<td>Fentanyl, midazolam, morphine</td>
<td>Continuous</td>
<td>SOS</td>
</tr>
<tr>
<td>Franck et al. (2012)¹</td>
<td>PICU (US)</td>
<td>N = 126</td>
<td>Not specified (converted to morphine &amp; midaz equivalents)</td>
<td>Bolus, continuous</td>
<td>WAT-1</td>
</tr>
<tr>
<td>Franck et al. (2008)¹⁰</td>
<td>PICU (US)</td>
<td>N = 83</td>
<td>Not specified (converted to morphine &amp; midaz equivalents)</td>
<td>Bolus, continuous</td>
<td>WAT-1, NRS of RN clinical judgment</td>
</tr>
<tr>
<td>Ista et al. (2008)³⁰</td>
<td>PICU (Netherlands)</td>
<td>N = 79</td>
<td>Fentanyl, midazolam, morphine</td>
<td>Continuous</td>
<td>SBOWC</td>
</tr>
<tr>
<td>Ducharme et al. (2005)³¹</td>
<td>PICU (Canada)</td>
<td>N = 27</td>
<td>Fentanyl, midazolam</td>
<td>Continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Franck et al. (2004)¹³</td>
<td>CICU (UK)</td>
<td>N = 15</td>
<td>Fentanyl, lorazepam, midazolam, morphine</td>
<td>Continuous</td>
<td>OBWS</td>
</tr>
<tr>
<td>Meyer &amp; Berens (2001)²¹</td>
<td>PICU (US)</td>
<td>N = 29</td>
<td>Fentanyl, lorazepam, methadone, morphine</td>
<td>Continuous, PO</td>
<td>NAS</td>
</tr>
<tr>
<td><strong>Retrospective Chart Review</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernández-Carrión et al. (2013)³⁶</td>
<td>PICU (Spain)</td>
<td>N = 48</td>
<td>Fentanyl, midazolam</td>
<td>Continuous</td>
<td>NAS</td>
</tr>
<tr>
<td>Johnson et al. (2010)³³</td>
<td>Academic hospital (US)</td>
<td>N = 15</td>
<td>Fentanyl, midazolam</td>
<td>Continuous, transdermal</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Bachiocco et al. (2006)²²</td>
<td>NICU (Italy)</td>
<td>N = 20</td>
<td>Fentanyl, morphine</td>
<td>Continuous</td>
<td>NAS, clinical judgment of NICU RNs and MDs</td>
</tr>
<tr>
<td>Tobias (2006)³⁹</td>
<td>PICU (US)</td>
<td>N = 7</td>
<td>Fentanyl, midazolam</td>
<td>Bolus, continuous</td>
<td>NAS</td>
</tr>
<tr>
<td>Weaning Method</td>
<td>IWS Incidence (N, %)</td>
<td>Risk Factors</td>
<td>Study Quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>-------------------------------------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>Low-dose: 9/41 (22%);</td>
<td>Dose; duration</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-dose: 4/37 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>Intervention: 1/21 (5%);</td>
<td>Dose; sedation protocol</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control: 7/20 (35%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>74/154 (48%)</td>
<td>Age; dose; duration; drug choice</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>21/126 (17%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>53/83 (64%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>27/79 (34%)</td>
<td>Dose; duration</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Not reported</td>
<td>Duration; sedation protocol</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>13/15 (87%)</td>
<td>Dose; drug choice</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>3/29 (10%)</td>
<td>Criticality; dose</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>24/48 (50%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard protocol</td>
<td>7/15 (47%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>3/20 (15%)</td>
<td>Criticality</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>N/A</td>
<td>Dose; mode of administration</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Site</td>
<td>Sample Size</td>
<td>Medications</td>
<td>Mode of Administration</td>
<td>IWS Assessment</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------</td>
<td>-------------</td>
<td>-------------------------------------------------</td>
<td>------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Siddappa et al. (2003)</td>
<td>PICU (US) N = 30</td>
<td></td>
<td>Fentanyl, lorazepam, midazolam, methadone, sufentanil, remifentanil</td>
<td>Continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Jacobs et al. (2001)</td>
<td>PICU (US) N = 133</td>
<td></td>
<td>Fentanyl, lorazepam, midazolam, morphine</td>
<td>Continuous</td>
<td>Clinical judgment of PICU RNs and MDs</td>
</tr>
<tr>
<td>Lugo et al. (2001)</td>
<td>PICU N = 22</td>
<td></td>
<td>Fentanyl, midazolam, methadone</td>
<td>Continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Fonsmark et al. (1999)</td>
<td>Med-surg ICU (Denmark) N = 40</td>
<td></td>
<td>Midazolam, morphine, pentobarbital</td>
<td>Bolus, continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Carnevale &amp; Ducharme</td>
<td>PICU (Canada) N = 5</td>
<td></td>
<td>Fentanyl, midazolam, morphine</td>
<td>Bolus, continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>Sheridan et al. (1994)</td>
<td>Burn unit (US) N = 24</td>
<td></td>
<td>Midazolam, morphine</td>
<td>Continuous</td>
<td>Clinical judgment of MDs</td>
</tr>
<tr>
<td>Bergman et al. (1991)</td>
<td>ICU (US) N = 45</td>
<td></td>
<td>Fentanyl, midazolam</td>
<td>Bolus, continuous</td>
<td>Physiologic s/sx</td>
</tr>
</tbody>
</table>

**Surveys**

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Sample Size</th>
<th>Medications</th>
<th>Mode of Administration</th>
<th>IWS Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenkins et al. (2007)</td>
<td>PICU (Multi-site, UK) N = 20</td>
<td></td>
<td>24 different agents reported</td>
<td>Bolus, continuous</td>
<td>Clinical judgment of PICU MDs</td>
</tr>
<tr>
<td>Twite et al. (2004)</td>
<td>PICU (Multi-site, US) N = 35</td>
<td></td>
<td>Fentanyl, lorazepam, midazolam, morphine</td>
<td>Continuous</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Legend of abbreviations (*listed alphabetically*): CICU – Cardiac Intensive Care Unit; CT – cardiothoracic; D/C – discontinuation; ICU – Intensive Care Unit; MDs – attending physicians; MNWS – Modified Narcotic Withdrawal Scale (adapted from Finnegan NAS monitoring tool); NAS – Finnegan’s Neonatal Abstinence Score; NICU – Neonatal Intensive Care Unit; NR – not reported; NRS – Numeric Rating Scale; OBWS – Opioid Benzodiazepine Weaning Scale; PICU – Pediatric Intensive Care Unit; PO – oral administration; RCT – randomized controlled trial; RN – registered nurse; s/sx – signs and symptoms; SBOWC – Sophia Benzodiazepine-Opioid Withdrawal Checklist; SOS – Sophia Observation withdrawal Symptoms scale; UK – United Kingdom; US – United States; WAT-1 – Withdrawal Assessment Tool-Version 1
### Cont’d from previous page

<table>
<thead>
<tr>
<th>Weaning Method</th>
<th>IWS Incidence (N, %)</th>
<th>Risk Factors</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard protocol</td>
<td>10/30 (33%)</td>
<td>Duration; drug choice</td>
<td>Moderate</td>
</tr>
<tr>
<td>NR</td>
<td>34/133 (26%)</td>
<td>Age</td>
<td>Moderate</td>
</tr>
<tr>
<td>Standard protocol</td>
<td>1/22 (5%)</td>
<td>Duration; drug choice; mode of administration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Abrupt D/C</td>
<td>14/40 (35%)</td>
<td>Criticality; dose</td>
<td>Low</td>
</tr>
<tr>
<td>Variable</td>
<td>N/A</td>
<td>Dose; sedation protocol; systems factors</td>
<td>Low</td>
</tr>
<tr>
<td>NR</td>
<td>2/24 (8%)</td>
<td>Dose; duration; mode of administration</td>
<td>Low</td>
</tr>
<tr>
<td>Abrupt D/C</td>
<td>5/45 (11%)</td>
<td>Age; criticality; mode of administration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Variable</td>
<td>34/335 (10%)</td>
<td>Age; criticality; dose; drug choice</td>
<td>N/A</td>
</tr>
<tr>
<td>Variable</td>
<td>65.7% of fellowship directors</td>
<td>Drug choice; mode of administration</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 2-3. Articles on opioid therapy only

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Sample Size</th>
<th>Medications</th>
<th>Mode of Administration</th>
<th>Withdrawal Assessment Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Interventional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominguez et al. (2003)⁵</td>
<td>NICU (US)</td>
<td>N = 19</td>
<td>Fentanyl</td>
<td>Continuous</td>
<td>NAS</td>
</tr>
<tr>
<td><strong>Prospective Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al. (2013)¹⁶</td>
<td>PICU (US)</td>
<td>N = 26</td>
<td>Fentanyl, morphine</td>
<td>Bolus, continuous</td>
<td>WAT-1</td>
</tr>
<tr>
<td>Franck et al. (1998)⁴</td>
<td>NICU</td>
<td>N = 34</td>
<td>Fentanyl, morphine</td>
<td>Bolus, continuous</td>
<td>Opioid weaning flowsheet (adapted from NAS)</td>
</tr>
<tr>
<td>Dagan et al. (1994)²⁴</td>
<td>PICU (Canada)</td>
<td>N = 7</td>
<td>Morphine</td>
<td>Continuous</td>
<td>Physiologic s/sx</td>
</tr>
<tr>
<td>French &amp; Nocera (1994)²⁶</td>
<td>PICU (US)</td>
<td>N = 12</td>
<td>Fentanyl</td>
<td>Bolus, continuous</td>
<td>NAS</td>
</tr>
<tr>
<td>Katz et al. (1994)²⁷</td>
<td>PICU (US)</td>
<td>N = 23</td>
<td>Fentanyl</td>
<td>Continuous</td>
<td>NAS</td>
</tr>
<tr>
<td><strong>Retrospective Chart Review</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeffries et al. (2012)³⁸</td>
<td>PICU (Canada)</td>
<td>N = 43</td>
<td>Morphine, methadone</td>
<td>Bolus, continuous</td>
<td>WAT-1</td>
</tr>
<tr>
<td>Lane et al. (1991)¹⁵</td>
<td>PICU (US)</td>
<td>N = 13</td>
<td>Fentanyl</td>
<td>Continuous</td>
<td>Physiologic s/sx, clinical judgment of PICU MDs</td>
</tr>
<tr>
<td>Arnold et al. (1990)²⁸</td>
<td>NICU (US)</td>
<td>N = 37</td>
<td>Fentanyl, sufentanil</td>
<td>Continuous</td>
<td>NAS</td>
</tr>
</tbody>
</table>

Legend of abbreviations (*listed alphabetically*): MDs – attending physicians; NAS – Finnegan’s Neonatal Abstinence Score; NICU – Neonatal Intensive Care Unit; PICU – Pediatric Intensive Care Unit; RN – registered nurse; s/sx – signs and symptoms; UK – United Kingdom; US – United States; WAT-1 – Withdrawal Assessment Tool-Version 1
<table>
<thead>
<tr>
<th>Weaning Strategy</th>
<th>Incidence of IWS</th>
<th>Risk Factors</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard protocol</td>
<td>10/19 (53%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Variable</td>
<td>11/25 (44%)</td>
<td>Age; dose; duration; weaning protocol</td>
<td>Moderate</td>
</tr>
<tr>
<td>Standard protocol</td>
<td>Fent: 13/23 (57%); Morphine: 1/11 (9%)</td>
<td>Dose; drug choice; duration; mode of administration</td>
<td>Moderate</td>
</tr>
<tr>
<td>No weaning</td>
<td>2/7 (29%)</td>
<td>Dose</td>
<td>Low</td>
</tr>
<tr>
<td>Variable</td>
<td>6/12 (50%)</td>
<td>Dose; duration</td>
<td>Low</td>
</tr>
<tr>
<td>Standard protocol</td>
<td>13/23 (57%)</td>
<td>Dose; duration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Standard protocol</td>
<td>18/43 (42%)</td>
<td>Dose; weaning protocol; withdrawal assessment; systems factors</td>
<td>Moderate</td>
</tr>
<tr>
<td>Variable</td>
<td>5/13 (39%)</td>
<td>Age; drug choice; mode of administration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Variable</td>
<td>21/37 (57%)</td>
<td>Dose; duration</td>
<td>Low</td>
</tr>
</tbody>
</table>
Table 2-4. Articles on benzodiazepine therapy only

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Sample Size</th>
<th>Medications</th>
<th>Mode of Administration</th>
<th>Withdrawal Assessment Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Interventional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominguez et al. (2006)</td>
<td>PICU (US)</td>
<td>N = 29</td>
<td>Lorazepam</td>
<td>Continuous</td>
<td>Clinical judgment of PICU MDs</td>
</tr>
<tr>
<td><strong>Prospective Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes et al. (1994)</td>
<td>PICU (UK)</td>
<td>N = 53</td>
<td>Midazolam</td>
<td>Continuous</td>
<td>Clinical judgment of bedside and research RNs; non-validated s/sx checklist</td>
</tr>
</tbody>
</table>

Legend of abbreviations *(listed alphabetically)*: MDs – attending physicians; PICU – Pediatric Intensive Care Unit; RN – registered nurse; s/sx – signs and symptoms; UK – United Kingdom; US – United States
### Weaning Strategy

<table>
<thead>
<tr>
<th>Weaning Strategy</th>
<th>Incidence of IWS</th>
<th>Risk Factors</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard protocol</td>
<td>7/29 (24%)</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Variable</td>
<td>9/53 (17%)</td>
<td>Age; dose</td>
<td>Low</td>
</tr>
</tbody>
</table>
CHAPTER 3

TOLERANCE, PATTERNS OF WEANING, AND IATROGENIC WITHDRAWAL SYNDROME

Patterns of sedation weaning in critically-ill children recovering from acute respiratory failure

Kaitlin M. Best¹, MS, RN, Lisa A. Asaro², MS, Linda S. Franck³, PhD, RN, FAAN, David Wypij²,⁴,⁵, PhD, Martha A.Q. Curley¹,², PhD, RN, FAAN, for the RESTORE Baseline Study Investigators*

Affiliations: ¹University of Pennsylvania, Philadelphia, USA; ²Boston Children’s Hospital, Boston, USA; ³University of California, San Francisco, USA; ⁴Harvard Medical School, Boston, USA; ⁵Harvard T.H. Chan School of Public Health, Boston, USA

Address correspondence to: Martha A.Q. Curley, School of Nursing, University of Pennsylvania, 418 Curie Blvd #425, Philadelphia, PA 19104-4217 USA, Curley@nursing.upenn.edu, Office # 215-573-9449, Fax # 215-746-2737

Short title: Patterns of sedation weaning in critically-ill children

Funding Source: All phases of data collection in the RESTORE study were supported by an NIH grant, HL086622/HL086649.

Keywords: sedation; weaning; withdrawal assessment; WAT-1; opioid; benzodiazepine; RESTORE

Conflict of Interest: The authors declare that they have no conflict of interest.
Abstract

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

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

Setting: Twenty-two pediatric intensive care units across the United States.

Patients: The sample included 145 patients, aged 2 weeks to 17 years, mechanically ventilated for acute respiratory failure who received ≥5 consecutive days of opioid exposure.

Measurements and Main Results: Group comparisons were made between patients with an inconsistent weaning pattern, defined as a ≥20% increase in daily opioid dose after the start of weaning, and the remaining patients defined as having a consistent weaning pattern. Demographic and clinical characteristics, opioid tolerance, and iatrogenic withdrawal symptoms were evaluated. Sixty-six patients (46%) were inconsistently weaned; 79 patients were consistently weaned. Prior to weaning, inconsistently weaned patients received higher peak and cumulative doses and longer exposures to opioids and benzodiazepines, demonstrated more opioid tolerance (39% vs. 24%), and received more chloral hydrate and barbiturates compared to consistently weaned patients. During weaning, inconsistently weaned patients assessed for withdrawal had a higher incidence of Withdrawal Assessment Tool-Version 1 scores ≥3 (85% vs. 46%), and received more sedative classes compared to consistently weaned patients.
Conclusions: This study characterizes sedative administration practices for pediatric patients prior to and during weaning from sedation after critical illness. It provides a novel methodology for describing weaning in an at-risk pediatric population that may be helpful in future research on weaning strategies to prevent iatrogenic withdrawal syndrome.
Introduction

Most children supported on mechanical ventilation in the pediatric intensive care unit (PICU) receive opioids and benzodiazepines for sedation during the critical phase of their illness. Sedation is necessary to help the child mitigate the noxious effects of invasive therapies [1,2]. An estimated 16% to 35% of mechanically ventilated children become tolerant to sedative medications while in the PICU [3], defined as diminishing clinical effectiveness of a drug over the course of treatment [4,5]. However, as children recover from critical illness sedative medications are discontinued or weaned over time. The amount of time spent weaning is a balance between keeping a child comfortable and free from significant withdrawal symptoms that can complicate recovery and minimizing PICU and hospital lengths of stay [5,6]. Abrupt discontinuation or too rapid weaning of opioids and/or benzodiazepines in physically dependent children results in iatrogenic withdrawal syndrome (IWS), a cluster of physiologic signs and symptoms that includes nervous system hyperirritability, autonomic system dysregulation, gastrointestinal dysfunction, and motor abnormalities [4,5,7,8].

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

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

Materials and Methods

Design: This study was a secondary analysis conducted on prospective data from the baseline, pre-randomization phase of the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) clinical trial. RESTORE was a multicenter
study designed to test a sedation management protocol in critically-ill pediatric patients with acute respiratory failure, defined as acute lung disease involving the airway and/or lung parenchyma [19]. During the baseline, pre-randomization phase (January to July 2009), all enrolled patients received usual care in 22 participating centers, but each PICU implemented the same pediatric-specific assessment tools for pain, sedation and IWS [20,21]. Sedation management was otherwise unrestricted. Institutional Review Board approval was obtained from each participating site. Consent for data collection was obtained from the parents and/or legal guardians of each patient.

**Study population:** Patients aged 2 weeks (≥42 weeks postmenstrual age) to 17 years were included if they were intubated and mechanically ventilated for acute respiratory failure [19]. This analysis was restricted to baseline phase patients exposed to ≥5 consecutive days of opioids from continuous infusions, scheduled intermittent, or as needed bolus doses; who completed opioid weaning within the 28-day data collection period without transfer or redirection of care; and who survived to hospital discharge. This restriction allowed for the full evaluation of a patient’s completed course of sedation therapy and the identification of individual patient patterns of wean from sedation.

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

Medication data included receipt of neuromuscular blockade, cumulative and peak daily opioid dosage (in morphine equivalents per kg of body weight), cumulative and peak daily benzodiazepine dosage collected to the end of opioid weaning (in midazolam equivalents per kg of body weight), and administration of any other sedative medications (e.g., chloral hydrate, clonidine, dexmedetomidine, ketamine, pentobarbital, phenobarbital, and propofol). Daily and cumulative sedative medication doses were compared using standard equivalencies [19]. Specifically, morphine equivalent conversion factors to equal 1mg morphine sulfate were as follows: 15µg remifentanil; 15µg fentanyl; 0.15mg hydromorphone; and 0.3mg methadone. Midazolam equivalent conversion factors to equal 1mg midazolam were: 0.2mg clonazepam; 0.3mg lorazepam; and 2mg diazepam. Sedative data were collected daily from endotracheal intubation, initiation of assisted breathing for patients with tracheostomies, or PICU admission for patients intubated at an outside hospital (Day 0) until 72 hours after their last opioid dose, hospital discharge, or Day 28 (whichever occurred first). Thresholds for opioid and benzodiazepine exposure from previous investigations of IWS were examined
Tolerance to the sedative effect of opioids was defined as a doubling of the Day 2 opioid dose prior to the start of weaning, an adaptation of Anand et al. [3] who defined tolerance as a doubling of the initially effective dose received during the first 24 hours of therapy. Using Day 2 data provided a more conservative approach to quantifying tolerance in cases where subjects may have been started on sub-optimal initial doses and required titration to achieve clinical effect.

Patients were assessed for signs of IWS using the Withdrawal Assessment Tool – Version 1 (WAT-1) [20,26]. The WAT-1 is an 11-item (12-point) instrument that includes a review of the patient’s medical record for the past 12 hours; direct observation of the patient for 2 minutes pre-stimulation; patient response to stimulation [27]; and assessment of post-stimulus recovery [26]. WAT-1 scoring was to be completed at least every 12 hours while the patient was in the PICU, and at least daily while in the hospital, from the day opioid weaning commenced until 72 hours after the patient received the last opioid dose. The highest daily WAT-1 score was used in analyses, with scores ≥3 being used as a validated cutoff for IWS from previous studies [20,26]. No recommendations were provided for patient management based on WAT-1 score during the baseline period.

**Weaning pattern:** Line graphs illustrating daily opioid and benzodiazepine doses and WAT-1 scores over the study period were constructed for each patient (L.A.A). Two investigators (L.S.F. and M.A.Q.C.), blind to the clinical characteristics of each patient, independently reviewed each patient’s graph to make a preliminary determination regarding each patient’s weaning pattern. These observations were then used to construct a decision-making algorithm (K.M.B.) for verifying, assigning, or reassigning the patient’s clinician-reported start of opioid weaning (Figure 3-1). Assignment of the start
of opioid weaning was necessary for patients with missing data. In addition, the clinician-reported start of opioid weaning may have been unreliable in cases where there was >2 day difference between the start of weaning and the day of peak dose. The start of opioid weaning was reassigned if (1) the clinician-reported start of weaning occurred >2 days before a peak opioid dose and/or (2) methadone was started >2 days before the clinician-reported start of weaning.

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

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

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

The median opioid start of weaning was 6 days (interquartile range [IQR]: 5-8 days), and 66 patients (46%) were inconsistently weaned. The start of opioid weaning occurred later for patients with an inconsistent pattern of weaning compared to patients with a consistent pattern of weaning (median; IQR: Day 6; 5-9 vs Day 5; 5-7; P=0.006). Figure 3-2 illustrates graphs of representative patients with consistent and inconsistent patterns of weaning.

Patient characteristics are shown in Table 3-1. There were no significant differences in baseline demographic or clinical characteristics between patients with inconsistent and consistent patterns of weaning. Patients with an inconsistent pattern of weaning experienced a longer duration of mechanical ventilation and PICU and hospital lengths of stay when compared to patients who were weaned consistently. Patients with an inconsistent pattern of weaning also had higher total cumulative opioid (median; IQR: 35.7 mg/kg; 17.4-61.2 vs 16.5 mg/kg; 7.4-25.5; P<0.001) and benzodiazepine doses (28.3 mg/kg; 11.2-65.0 vs 12.8 mg/kg; 5.7-22.2; P<0.001) than patients with a consistent pattern of weaning.
Preweaning exposure: Characteristics of opioid and benzodiazepine exposure in the preweaning period are shown in Table 3-2. The majority of patients in both groups received fentanyl and midazolam as their primary opioid and benzodiazepine agents. In the preweaning period, patients with an inconsistent pattern of weaning received higher preweaning daily peak and cumulative doses of opioids and benzodiazepines and had longer durations of exposure to opioids and benzodiazepines. Patients with an inconsistent weaning pattern were also more likely to have developed tolerance to opioids, and to have received a total midazolam dose >60 mg/kg prior to the start of weaning. Inconsistently weaned patients were more likely to have received chloral hydrate and barbiturates. There were no significant differences between groups in the number of patients receiving methadone, clonidine, dexmedetomidine, ketamine, or propofol prior to the start of opioid weaning.

Exposure during weaning: Characteristics of opioid and benzodiazepine exposure during weaning are shown in Table 3-3. The percent decrease in daily opioid dose over the first 24 and 48 hours after the initiation of weaning was lower among patients with inconsistent patterns of weaning. Inconsistently weaned patients received more opioid boluses and received boluses for significantly more days during the weaning period. A greater proportion of patients with an inconsistent pattern of weaning received methadone, clonidine, dexmedetomidine, chloral hydrate, and barbiturates during the weaning period. One hundred twelve (77%) patients were assessed for withdrawal symptoms using the WAT-1. More patients with an inconsistent pattern of weaning had WAT-1 assessments performed during the weaning period, had WAT-1 scores ≥3, and had higher peak WAT-1 scores. Among patients with WAT-1 assessments, tolerance to
opioids was observed more frequently in patients who ever had WAT-1 scores ≥3, compared to patients who always scored <3 (37% vs 19%; P=0.02).

Discussion

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

Our findings align with previous research, which showed that higher cumulative and peak doses of opioids and benzodiazepines and longer exposures are associated with IWS [6,10-13,16,20,28]. However, our data are the first to quantify their associations with an inconsistent weaning pattern. While intuitive, these findings suggest that current weaning practices should be more critically examined, not only for the rate of dose reductions but also for consistency. Of note, our two patterns of weaning could not be differentiated by previously published threshold doses of fentanyl that have been associated with IWS. These published thresholds included sedative doses received after the start of weaning [6,10,11], a criterion that limits their prognostic utility for weaning outcomes.
In this study, more patients with an inconsistent pattern of weaning met criteria for opioid tolerance. Typically, the focus of opioid tolerance is placed on the escalation of sedation therapy and not necessarily on sedation weaning. Only one previous study reported using a standard definition of opioid tolerance when describing the weaning process [3], which was adapted for this analysis. Future studies can apply this easily computed definition of opioid tolerance, that is, a doubling of the Day 2 opioid dose to achieve the same therapeutic effect over the acute preweaning phase of illness, when planning how best to wean patients from sedation.

During the first 24 and 48 hours of weaning, consistently weaned patients tolerated a greater percent drop in their daily opioid dose. In addition, our data show wide variation in the percent drop experienced by patients during opioid weaning, even when unit-based weaning protocols were reported to be in place. Patients with an inconsistent pattern of weaning received significantly more opioid rescue bolus doses for a greater number of days during the weaning period, beginning with the day of the start of weaning. This result may indicate that signs of IWS were first observed soon after the start of weaning.

Examination of WAT-1 scores showed that more inconsistently weaned patients with assessments had peak WAT-1 scores ≥3. It is interesting to note that patients with inconsistent patterns of weaning experienced greater frequency and severity of WAT-1 scores despite receiving significantly more doses of methadone, clonidine, dexmedetomidine, chloral hydrate, and barbiturates during the weaning period.

This study has some limitations, the most significant of which is that the findings cannot offer evidence for causation. The question of whether inconsistent weaning
patterns are the outcome of preweaning risk factors or a contributory cause of higher WAT-1 scores and more intensive or protracted weaning remains unanswered. In particular, not all patients were assessed for IWS, which may have caused an ascertainment bias in the observed association between inconsistent weaning and IWS. Without a complete picture of benzodiazepine weaning in this dataset or a definition of benzodiazepine tolerance, it is impossible to draw conclusions about tolerance to benzodiazepines among patients in this study. It is possible that patients became tolerant to both opioids and benzodiazepines, especially since more inconsistently weaned patients received preweaning benzodiazepine doses >60 mg/kg, a threshold associated with IWS [14]. As in previous studies [7,26], it is impossible to parse the effects of these medications, since most patients received both concurrently. Finally, the available data offers little insight into the clinical practices or environment in which children were undergoing recovery and weaning, or the effects of either sedation therapy or the environment on restorative sleep, both of which may have been contributory to increased sedative needs in certain patients [29,30]. These considerations will require further research.

Conclusion

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

RESTORE Baseline Study Investigators include Geoffrey L. Allen (Children's Mercy Hospital, Kansas City, MO); Judy A. Ascenzi (The Johns Hopkins Hospital, Baltimore, MD); Scot T. Bateman (University of Massachusetts Memorial Children's Medical Center, Worcester, MA); Santiago Borasino (Children’s Hospital of Alabama, Birmingham, AL); Ira M. Cheifetz (Duke Children’s Hospital, Durham, NC); Allison S. Cowl (Connecticut Children's Medical Center, Hartford, CT); E. Vincent S. Faustino (Yale-New Haven Children’s Hospital, New Haven, CT); Lori D. Fineman (University of California San Francisco Benioff Children’s Hospital at San Francisco, San Francisco, CA); Heidi R. Flori (University of California at San Francisco Benioff Children's Hospital at Oakland, Oakland, CA); Mary Jo C. Grant (Primary Children’s Hospital, Salt Lake City, UT); James H. Hertzog (Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE); Larissa Hutchins (The Children's Hospital of Philadelphia, Philadelphia, PA); Aileen L. Kirby (Oregon Health & Science University Doernbecher Children's Hospital, Portland, OR); JoAnne E. Natale (University of California Davis Children’s Hospital, Sacramento, CA); Phineas P. Oren (St. Louis Children’s Hospital, St. Louis, MO); Nagendra Polavarapu (Advocate Children’s Hospital-Oak Lawn, Oak Lawn, IL); Thomas P. Shanley (C. S. Mott Children’s Hospital at the University of Michigan, Ann Arbor, MI); Shari Simone (University of Maryland Medical Center, Baltimore, MD); Lauren R. Sorce (Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL); Michele A. Vander Heyden (Children's Hospital at Dartmouth, Dartmouth, NH).
References


Figure 3-1. Start of weaning decision algorithm

Note: The algorithm assigned the start of opioid weaning for 42 patients (29%) missing data on the clinician-reported start of weaning. For the remaining 103 patients, the clinician-reported start of weaning was verified by the algorithm for 78 patients (76%) and reassigned for 25 patients (24%).
Figure 3-2. Opioid weaning patterns

Representative graphs of daily opioid and benzodiazepine doses among patients with consistent (A) and inconsistent (B) patterns of opioid weaning. Note: The first vertical line marks the day of the peak opioid dose, while the second vertical line represents the start of the opioid weaning period.
Table 3-1. Patient characteristics by pattern of weaning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Consistent Wean (N=79)</th>
<th>Inconsistent Wean (N=66)</th>
<th>P Value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at PICU admission – years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) – years</td>
<td>2.0 (0.4-8.3)</td>
<td>1.4 (0.3-4.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>2 weeks to 1.99 years – no. (%)</td>
<td>40 (51)</td>
<td>37 (56)</td>
<td>0.16</td>
</tr>
<tr>
<td>2.00 to 5.99 years</td>
<td>11 (14)</td>
<td>15 (23)</td>
<td></td>
</tr>
<tr>
<td>6.00 to 17.99 years</td>
<td>28 (35)</td>
<td>14 (21)</td>
<td></td>
</tr>
<tr>
<td>Female – no. (%)</td>
<td>45 (57)</td>
<td>33 (50)</td>
<td>0.49</td>
</tr>
<tr>
<td>Non-Hispanic white – no./total no. (%)</td>
<td>45/76 (59)</td>
<td>43/64 (67)</td>
<td>0.52</td>
</tr>
<tr>
<td>Baseline PCPC=1 – no. (%)</td>
<td>62 (78)</td>
<td>48 (73)</td>
<td>0.28</td>
</tr>
<tr>
<td>Baseline POPC=1 – no. (%)</td>
<td>61 (77)</td>
<td>45 (68)</td>
<td>0.11</td>
</tr>
<tr>
<td>Able to verbally communicate pain at baseline – no./total no. (%)</td>
<td>31/44 (70)</td>
<td>29/34 (85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRISM III-12 score – median (IQR)</td>
<td>6 (2-12)</td>
<td>6 (3-12)</td>
<td>0.44</td>
</tr>
<tr>
<td>Percent risk of mortality based on PRISM III-12 score – median (IQR)</td>
<td>2 (1-12)</td>
<td>3 (1-13)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Primary reason for intubation – no. (%)</strong></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31 (39)</td>
<td>28 (42)</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>23 (29)</td>
<td>16 (24)</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure related to sepsis</td>
<td>6 (8)</td>
<td>7 (11)</td>
<td></td>
</tr>
<tr>
<td>Asthma or reactive airway disease</td>
<td>5 (6)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>4 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (13)</td>
<td>9 (14)</td>
<td></td>
</tr>
<tr>
<td>PARDS based on Day 1 OI or OSI – no. (%)^d</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>At risk (OI &lt;4.0 or OSI &lt;5.0)</td>
<td>28 (35)</td>
<td>23 (35)</td>
<td></td>
</tr>
<tr>
<td>Mild (OI 4.0-7.9 or OSI 5.0-7.4)</td>
<td>24 (30)</td>
<td>17 (26)</td>
<td></td>
</tr>
<tr>
<td>Moderate (OI 8.0-16.0 or OSI 7.5-12.3)</td>
<td>18 (23)</td>
<td>19 (29)</td>
<td></td>
</tr>
<tr>
<td>Severe (OI &gt;16.0 or OSI &gt;12.3)</td>
<td>9 (11)</td>
<td>7 (11)</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blockade for the entire duration of Days 0 to 2 – no. (%)</td>
<td>3 (4)</td>
<td>5 (8)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Any past medical history – no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurity (&lt;36 weeks post-menstrual age)</td>
<td>10 (13)</td>
<td>5 (8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Asthma (prescribed bronchodilators or steroids)</td>
<td>12 (15)</td>
<td>10 (15)</td>
<td>0.96</td>
</tr>
<tr>
<td>Seizure disorder (prescribed anticonvulsants)</td>
<td>11 (14)</td>
<td>6 (9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Neurologic/neuromuscular disorder which places patient at risk for aspiration</td>
<td>8 (10)</td>
<td>7 (11)</td>
<td>0.83</td>
</tr>
<tr>
<td>Cancer (current or past diagnosis)</td>
<td>1 (1)</td>
<td>5 (8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Known chromosomal abnormality</td>
<td>3 (4)</td>
<td>4 (6)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Hospital Course</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation – days, median (IQR)</td>
<td>5.9 (4.7-8.2)</td>
<td>9.1 (6.3-11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PICU length of stay – days, median (IQR)</td>
<td>9.3 (6.9-12.7)</td>
<td>12.8 (9.5-17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital length of stay – days, median (IQR)</td>
<td>14 (10-20)</td>
<td>21.5 (16-26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQR, interquartile range; OI, oxygenation index; OSI, oxygen saturation index; PARDS, pediatric acute respiratory distress syndrome; PCPC, Pediatric Cerebral Performance Category; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category; PRISM III-12, Pediatric Risk of Mortality III score from first 12 hours in the PICU.
P values for the comparison of patients with consistent vs. inconsistent weaning patterns were calculated using linear, cumulative logit, logistic, and proportional hazards regression accounting for site as a cluster variable using generalized estimating equations for log-transformed continuous, ordinal, binary, and time-to-event variables, respectively.

PCPC and POPC range from 1 to 6, with higher categories indicating greater impairment.

Able to verbally communicate pain at baseline includes only patients aged 16 months and older.

Oxygenation index (OI) was calculated as \([\left(FIO_2 \times \text{mean airway pressure}\right)/\text{PaO}_2 \times 100]\). When an arterial blood gas was not available, \(\text{SpO}_2\) was used to estimate \(\text{PaO}_2\) in order to calculate oxygen saturation index (OSI) \([\left(FIO_2 \times \text{mean airway pressure}\right)/\text{SpO}_2 \times 100]\). Lower scores reflect better oxygenation.
Table 3-2. Opioid and benzodiazepine exposure pre-opioid weaning by pattern of weaning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Consistent Wean (N=79)</th>
<th>Inconsistent Wean (N=66)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary opioid agent preweaning – no. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>58 (73)</td>
<td>47 (71)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>21 (27)</td>
<td>18 (27)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Opioid exposure preweaning – mg/kg, median (IQR)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak daily dose</td>
<td>3.4 (1.7-5.7)</td>
<td>5.0 (2.6-7.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>13.4 (6.4-21.7)</td>
<td>19.8 (9.7-39.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cumulative dose – morphine only</td>
<td>0.1 (0-1.3)</td>
<td>0.4 (0-2.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cumulative dose – fentanyl only, mcg/kg</td>
<td>187.8 (3.1-319.0)</td>
<td>196.7 (16.2-433.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Exposure days – median (IQR)</td>
<td>5 (3-6)</td>
<td>6 (5-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary benzodiazepine agent pre-opioid weaning – no. (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.52&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Midazolam</td>
<td>59 (75)</td>
<td>51 (77)</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>18 (23)</td>
<td>15 (23)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine exposure pre-opioid weaning – mg/kg, median (IQR)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak daily dose</td>
<td>2.7 (1.5-4.9)</td>
<td>4.1 (1.6-7.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>9.6 (4.6-17.6)</td>
<td>15.4 (6.1-38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exposure days – median (IQR)</td>
<td>5 (3-6)</td>
<td>6 (5-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of Day 2 opioid dose pre-opioid weaning – no. (%)</td>
<td>19 (24)</td>
<td>26 (39)</td>
<td>0.01</td>
</tr>
<tr>
<td>Thresholds pre-opioid weaning – no. (%)&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fentanyl &gt;2.5 mg/kg or &gt;9 days&lt;sup&gt;11&lt;/sup&gt;</td>
<td>6 (8)</td>
<td>9 (14)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total fentanyl &gt;1.6 mg/kg or &gt;5 days&lt;sup&gt;12&lt;/sup&gt;</td>
<td>23 (29)</td>
<td>27 (41)</td>
<td>0.14</td>
</tr>
<tr>
<td>Total fentanyl &gt;1.2 mg/kg&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0</td>
<td>4 (6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total midazolam &gt;60 mg/kg&lt;sup&gt;15&lt;/sup&gt;</td>
<td>0</td>
<td>11 (17)</td>
<td>0.005</td>
</tr>
<tr>
<td>Other sedatives pre-opioid weaning – no. (%)&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>6 (8)</td>
<td>10 (15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0</td>
<td>1 (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>12 (15)</td>
<td>16 (24)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ketamine</td>
<td>11 (14)</td>
<td>10 (15)</td>
<td>0.92</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>7 (9)</td>
<td>14 (21)</td>
<td>0.01</td>
</tr>
<tr>
<td>Propofol</td>
<td>10 (13)</td>
<td>3 (5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>3 (4)</td>
<td>9 (14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Number of sedative classes received pre-opioid weaning – median (IQR)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>0.07</td>
</tr>
<tr>
<td>1 – no. (%)</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46 (58)</td>
<td>34 (52)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22 (28)</td>
<td>18 (27)</td>
<td></td>
</tr>
<tr>
<td>4-7</td>
<td>9 (11)</td>
<td>14 (21)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, interquartile range.

<sup>a</sup> P values for the comparison of patients with consistent vs. inconsistent weaning patterns were calculated using logistic, linear, and proportional hazards regression accounting for site as a
cluster variable using generalized estimating equations for binary, log-transformed continuous, and time-to-event variables, respectively. Where there was a zero count in the consistent wean group, the P value was calculated with the use of a stratified exact test with adjustment for site.

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

9 This P value compares primary agent morphine vs. fentanyl.

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

9 Benzodiazepine data was collected until study discharge, which was based on the end of opioid exposure; thus patients may have still been receiving benzodiazepines at study discharge. Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2). Excludes 9 patients (6 consistent, 3 inconsistent) who did not wean from benzodiazepines.

f This P value compares primary agent midazolam vs. lorazepam.

8 Different sedative classes include opioids, benzodiazepines, alpha2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.
Table 3-3. Opioid and benzodiazepine exposure during opioid weaning by pattern of weaning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Consistent Wean (N=79)</th>
<th>Inconsistent Wean (N=66)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid exposure during weaning – mg/kg, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak daily dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.9 (0.1-2.7)</td>
<td>3.0 (1.0-5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5 (0.1-4.3)</td>
<td>11.5 (3.9-19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exposure days – median (IQR)</td>
<td>2 (1-5)</td>
<td>10.5 (8-13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Benzodiazepine exposure during opioid weaning – mg/kg, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak daily dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.1 (0.1-2.6)</td>
<td>2.3 (1.2-5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.5 (0.3-4.5)</td>
<td>9.0 (2.7-19.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent drop in daily opioid dose from start of wean to next day – median (IQR)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>47 (0-100)</td>
<td>24 (–10-57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent drop in daily opioid dose from start of wean to 2 days later – median (IQR)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>82 (13-100)</td>
<td>42 (–2-81)</td>
<td>0.02</td>
</tr>
<tr>
<td>Received opioid bolus doses during weaning – no. (%)</td>
<td>50 (63)</td>
<td>57 (86)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of days patient received opioid bolus doses – median (IQR)</td>
<td>1 (1-2)</td>
<td>3 (2-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other sedatives during opioid weaning – no. (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>15 (19)</td>
<td>37 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1 (1)</td>
<td>8 (12)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>14 (18)</td>
<td>23 (35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ketamine</td>
<td>4 (5)</td>
<td>5 (8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>3 (4)</td>
<td>7 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Propofol</td>
<td>6 (8)</td>
<td>7 (11)</td>
<td>0.64</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2 (3)</td>
<td>6 (9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of sedative classes received during opioid weaning – median (IQR)</td>
<td>2 (1-3)</td>
<td>2 (2-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0, no. (%)</td>
<td>7 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (16)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>39 (49)</td>
<td>31 (47)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14 (18)</td>
<td>16 (24)</td>
<td></td>
</tr>
<tr>
<td>4-7</td>
<td>6 (8)</td>
<td>15 (23)</td>
<td></td>
</tr>
<tr>
<td>WAT-1 assessments performed during opioid weaning – no. (%)</td>
<td>50 (63)</td>
<td>62 (94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WAT-1 ever ≥ 3 – no./total no. (%)</td>
<td>23/50 (46)</td>
<td>53/62 (85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak WAT-1 score – median (IQR)</td>
<td>2 (1-5)</td>
<td>5 (4-6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQR, interquartile range; WAT-1, Withdrawal Assessment Tool – Version 1.
<sup>a</sup> P values for the comparison of patients with consistent vs. inconsistent weaning patterns were calculated using linear, proportional hazards, and logistic regression accounting for site as a cluster variable using generalized estimating equations for log-transformed continuous, time-to-event, and binary variables, respectively. Percent drop variables were not log-transformed due to negative values.
<sup>b</sup> Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanil (0.015).
\(^c\) Benzodiazepine data was collected until study discharge, which was based on the end of opioid exposure; thus patients may have still been receiving benzodiazepines at study discharge. Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

\(^d\) Excludes 2 consistently weaned patients who started weaning on day 5 and were study discharged that day.

\(^e\) Different sedative classes include opioids, benzodiazepines, alpha2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.
CHAPTER 4

A PREDICTIVE MODEL OF RISK FOR IATROGENIC WITHDRAWAL SYNDROME

Patient, process and system predictors of iatrogenic withdrawal syndrome in critically ill children

Kaitlin M. Best, PhD(c), MS, RN
David Wypij, PhD
Lisa A. Asaro, MS
Martha A. Q. Curley, PhD, RN, FAAN

for the RESTORE Study Investigators

Affiliations: 1School of Nursing, University of Pennsylvania; 2Department of Cardiology, Boston Children’s Hospital; 3Department of Pediatrics, Harvard Medical School; 4Department of Biostatistics, Harvard T.H. Chan School of Public Health; 5Department of Anesthesiology and Critical Care Medicine, Perelman School of Medicine, University of Pennsylvania; 6Cardiovascular and Critical Care Program, Boston Children’s Hospital

Corresponding Author:
Martha A. Q. Curley
University of Pennsylvania School of Nursing
418 Curie Blvd, Rm #425
Philadelphia, PA 19104
curley@nursing.upenn.edu

Contributor’s Statements:
Kaitlin M. Best: Ms. Best conceptualized and designed the study, carried out the analyses, drafted and revised the manuscript and approved the final manuscript as submitted.
David Wypij: Dr. Wypij supervised and consulted on analyses, critically reviewed the manuscript and approved the final manuscript as submitted.
Lisa A. Asaro: Ms. Asaro generated the study dataset from the parent study database, consulted on initial analyses, critically reviewed the manuscript and approved the final manuscript as submitted.
Martha A. Q. Curley: Dr. Curley supervised the conceptualization of the study and conduct of the analysis, critically reviewed the manuscript and approved the final manuscript as submitted.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Funding Sources: All phases of data collection in the RESTORE study were supported by NIH grant HL086622/HL086649 (PIs: Curley & Wypij). The conduct of this secondary analysis was supported by NIH grant F31NR015172 (PI: Best).

Running head: Prediction of IWS risk in critically ill children

Subject category: 4.11 (Pediatric Critical Care)

At a Glance Commentary: We provide new evidence for younger age, pre-existing cognitive impairment and higher nursing workload as risk factors for iatrogenic withdrawal syndrome, as well as confirming previously identified associations with dose and duration of sedative exposure. As the largest study of iatrogenic withdrawal syndrome in critically ill children to date, this is also the first study to characterize system-level influences on this outcome. The identified risk factors could inform future practice in sedation management and weaning.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.
Abstract

Rationale: Sedation use in pediatric critical illness is associated with iatrogenic withdrawal syndrome during recovery. Little is known about risk factors for iatrogenic withdrawal beyond sedative dose and exposure time.

Objectives: To create a predictive model of patient, process and system risk factors for iatrogenic withdrawal in critically ill pediatric patients who received ≥5 days of sedation.

Methods: Secondary analysis of prospective data from a clinical trial of nurse-led, goal-directed sedation management. Logistic regression with generalized estimating equations to account for clustering by site was used to evaluate risk factors for iatrogenic withdrawal.

Measurements and Main Results: Iatrogenic withdrawal was defined as having at least two Withdrawal Assessment Tool-1 scores ≥3 after the start of opioid weaning. Eligible subjects with iatrogenic withdrawal (544/1157; 47%) were younger and more likely to have pre-existing cognitive or functional impairment. Subjects with iatrogenic withdrawal received higher sedative doses and longer exposure periods. In multivariable analyses, significant predictors of iatrogenic withdrawal included younger age (OR 2.73, p<0.001), pre-existing cognitive impairment (OR 1.98, p<0.001), higher preweaning mean daily opioid dose (OR 1.39, p<0.001), longer duration of sedation (OR 1.07, p=0.046), receipt of three or more preweaning sedative classes (OR 1.39, p<0.001), higher nursing workload (OR 1.68, p=0.004) and receiving care at sites with higher proportions of 1:1 nurse staffing (OR 1.15, p=0.002).

Conclusions: Iatrogenic withdrawal syndrome is common in children recovering from critical illness and several risk factors are predictive. High-risk patients could be
identified before starting weaning to better prevent iatrogenic withdrawal among at-risk patients.

Key words: Opioid; benzodiazepine; sedation; WAT-1; _RESTORE_
Introduction

Although opioids and benzodiazepines are routinely used to achieve analgesia and sedation in critically ill pediatric patients, they may also cause untoward effects. In particular, iatrogenic withdrawal syndrome (IWS) can cause discomfort for patients, increased sedation exposure and prolonged duration of mechanical ventilation and lengths of stay.\(^1,2\) IWS is a constellation of signs and symptoms spanning three physiologic domains – autonomic dysfunction, gastrointestinal disturbances and neurologic and motor abnormalities – that manifest following rapid weaning or abrupt cessation of sedation therapy in physically dependent patients.\(^1,3,4\) Up to 57% of critically ill children in the pediatric intensive care unit (PICU) who receive opioids or benzodiazepines may exhibit signs and symptoms of IWS,\(^5–7\) a figure that increased to nearly 80% in a cohort of infants who had undergone extracorporeal membrane oxygenation (ECMO) or cardiac surgery.\(^8\)

To date, the majority of research on IWS has focused on characterizing its signs and symptoms\(^3,4,9,10\) and elucidating its association with threshold sedative exposures,\(^5,7,11–14\) such as duration of opioid or benzodiazepine therapy exceeding five days\(^7,13\) and cumulative doses greater than 1.6 mg/kg of fentanyl\(^5,7\) or 60 mg/kg of midazolam.\(^14\) Yet a clinical profile of the patient at risk for IWS is still lacking. Most previous studies have been limited by single center, retrospective designs and/or small samples. Younger\(^12,15,16\) or female\(^15\) patients with a greater severity of illness,\(^15\) including neurologic involvement,\(^17,18\) may be more likely to experience IWS. However, these findings have been inconsistent across published reports,\(^19,20\) at least in part due to a lack of standardization in defining and assessing IWS.\(^21\)
Sedation management in the PICU occurs within a unique context that may also influence the development of IWS; however, little research has evaluated the process of sedation therapy or system-level determinants of related outcomes. For example, although most clinicians recognize the need to gradually wean patients from sedation therapy in order to prevent IWS, variation exists in the medications and doses used during sedation and weaning. Adherence to standardized sedation protocols including weaning algorithms and assessments for IWS is less than ideal, which may be a consequence of clinician factors or workflow constraints in busy PICUs. Little is known about system-level factors that may prevent the development of IWS in critically ill children.

These gaps have resulted in a limited understanding of why children continue to experience IWS despite the implementation of protocols to prevent it. We have proposed a conceptual model illustrating the potential contributions of different levels of risk factors that impact a critically ill child’s risk for experiencing IWS during recovery in the PICU. The purpose of this study was to apply this framework in generating a predictive model of risk factors for IWS at the levels of the patient, the process and the healthcare system. A comprehensive profile of the at-risk patient may enable primary prevention of this iatrogenic complication, including potential restructuring of processes and systems of care in order to optimize sedation therapy for children in the PICU.

Methods

Data source: This study was a secondary analysis of data from the Randomized Evaluation of Sedation Titration fOr Respiratory FailurE (RESTORE) clinical trial. RESTORE was a multicenter cluster randomized trial testing the impact of a nurse-led,
goal-directed sedation management protocol on length of mechanical ventilation in critically ill pediatric patients with acute respiratory failure. Subjects were enrolled at 31 sites from June 2009 to December 2013. Consent for prospective data collection was obtained from the subjects’ parents and/or legal guardians, and the institutional review board at each site approved the RESTORE study protocol.

**Study population:** Patients aged 2 weeks (≥42 weeks postmenstrual age) to 17 years were enrolled in the RESTORE trial if they were intubated and mechanically ventilated for acute respiratory failure. Detailed inclusion and exclusion criteria are published elsewhere. Eligible subjects for this secondary analysis included subjects from both the control and intervention groups who had ≥5 consecutive days of opioid exposure from continuous infusions, scheduled intermittent or as needed bolus doses. We excluded subjects who did not complete their course of sedative weaning within 28 days (i.e., non-survivors, transfers and study withdrawals).

**Variables and measures:** The primary outcome of IWS was defined as two or more Withdrawal Assessment Tool-1 (WAT-1) scores ≥3 after the start of opioid weaning. The WAT-1 is an 11-item (12-point) instrument that screens for signs and symptoms of opioid- and benzodiazepine-related IWS. Per protocol, subjects with ≥5 days of opioid therapy were assessed at least twice daily in the PICU, and at least daily while in the hospital, from the start of opioid weaning until 72 hours after the last opioid dose. A one-time WAT-1 score ≥3 has excellent sensitivity (87%) and specificity (88%) for detection of IWS. Requiring more than one WAT-1 score ≥3 was a conservative approach to avoid inclusion of false positives from subjects with isolated symptoms unrelated to IWS.
Data were collected daily from endotracheal intubation (Day 0) until 72 hours after the last opioid dose, hospital discharge or Day 28 (whichever occurred first). Medication data included daily dose and route of all sedative medications, until the start of opioid weaning. Patient- and process-level variables were defined as in the primary publication or according to operational definitions included in the online supplement. System-level variables were drawn from each site’s self-reported pre-randomization organizational assessment and the case report forms from each enrolled subject. Each subject was assigned values for the system-level variables from their site, with the exception of nursing workload. The Nine Equivalents of nursing Manpower use Score (NEMS) was calculated daily for each patient; possible scores ranged from 0 to 56, with higher scores representing increasing nursing workload. Median preweaning scores calculated for each subject were used for analysis.

**Analysis:** Subjects meeting eligibility criteria were dichotomized based on WAT-1 scores. Potential predictors of interest (Supplemental Table 4-5) were explored for differences between groups. Variance within and between centers was accounted for using generalized estimating equations with an independent working correlation structure and robust sandwich variance estimator. Site-level variables were weighted by the inverse variance of each site’s IWS rate, then Pearson correlations (for continuous predictors) and linear regressions (for binary predictors) were used to evaluate associations with the proportion of subjects with IWS. Log-transformations were used as necessary for non-normally distributed variables. An a priori threshold of p <0.2 was set for variables from bivariate analyses to be considered in the next stage of analysis. Multivariable logistic regression for model building used manual backward selection procedures and included...
generalized estimating equations to account for clustering by site. Variables with \( p < 0.05 \) were retained. It was anticipated that several variables would be highly correlated (e.g., medication dose and duration); therefore, assessment of collinearity using rank-order Spearman correlations \((r_s)\) was included in the modeling strategy. All analyses were conducted using Stata version 13 (Stata LP, College Station, TX).

Results

Of 2449 enrolled subjects from the RESTORE study cohort, 1170 subjects (48%) were excluded due to receiving \(<5\) consecutive days of opioid exposure \((n=767)\), incomplete sedative weaning by Day 28 \((n=309)\), transfer \((n=19)\) and death or redirection of care \((n=75)\). Of the 1279 remaining subjects, an additional 122 subjects (10%) were excluded because they did not have any WAT-1 assessments, leaving 1157 subjects for this analysis.

IWS was observed in 544 subjects (47%) distributed across 31 sites, although there was a wide range in IWS rates per site (range 20%-80%). The intraclass correlation coefficient (ICC) of IWS was 0.051 (95% CI 0.026-0.142) after adjusting for age group, severity of illness (i.e., Pediatric Risk of Mortality [PRISM] III-12 score) and baseline functional status (i.e., Pediatric Overall Performance Category [POPC] score). Subjects with IWS were younger and more likely to have pre-existing cognitive and functional impairment (Table 4-1). There was no difference in the proportion of subjects with IWS between the control and intervention arms.

Patient-level variables: Dose and duration of both opioid and benzodiazepine therapy were greater among subjects with IWS (Table 4-2). There was no difference in the incidence of IWS based on primary opioid or benzodiazepine agent used for sedation.
Opioid tolerance occurred more often in subjects with IWS. There were significant age-related differences in both mean daily opioid and benzodiazepine dose (p<0.001 for each), with infants less than six months of age and children over six years receiving lower doses per kilogram regardless of IWS outcome (Figure 4-1). Age-related differences were not observed in sedative duration (p=0.20).

**Process-level variables:** Patients with IWS tended to receive more classes of sedative medications prior to the start of weaning (Table 4-2) and were more likely to be inconsistently weaned (43% versus 26%, p≤0.001). Preweaning SBS assessment compliance was comparable between IWS and non-IWS subjects [median (interquartile range [IQR]): 86% (63-100) versus 80% (60-100); p=0.66].

**System-level variables:** Few PICU characteristics were significantly correlated with the rate of IWS per site (Table 4-3). Median NEMS scores were 27 (IQR 27-34) among subjects with IWS and 27 (IQR 27-33) in non-IWS subjects (p=0.07). Nurse to patient staffing ratios were moderately correlated with the rate of IWS, suggesting higher rates of IWS in PICUs with a greater proportion of one nurse to one patient assignments. Regardless of IWS outcome, lower cumulative opioid doses were administered to patients treated in PICUs with a greater proportion of one-to-one assignments compared to sites with a lower frequency of high staffing ratios, even after adjusting for average patient age, severity of illness, nursing workload and number of annual PICU admissions (p<0.001).

**Collinear variables:** Among the preweaning medication variables, cumulative opioid dose was strongly correlated with mean (r_s=0.93, p<0.001) and peak (r_s=0.90, p<0.001) daily opioid doses and with duration of sedative exposure (r_s=0.93, p<0.001).
Benzodiazepine variables showed similar relationships. Baseline PCPC and POPC scores were also strongly correlated ($r = 0.89$, $p<0.001$). In order to build a parsimonious and valid model, we restricted consideration to preweaning duration of sedative exposure, preweaning mean daily opioid dose and pre-existing cognitive impairment in multivariable modeling.

**Multivariable modeling:** The multivariable prediction model identified variables at the patient-, process- and system-levels with significant associations with IWS (**Table 4-4**). Each additional day of sedative exposure increased a subject’s odds of experiencing IWS. Subjects under six months of age had the highest odds of experiencing IWS compared to the oldest age group. Pre-existing cognitive impairment nearly doubled the odds of IWS. Process- and system-level risk factors included receiving additional sedative medications beyond an opioid and benzodiazepine, higher preweaning NEMS scores and more one-to-one nurse staffing. The c-statistic for the model including only variables with individual patient-level data was 0.63 (95% CI 0.60-0.66), which slightly improved to 0.65 (95% CI 0.62-0.68) with the addition of the system-level variable. Although a greater number of subjects with IWS developed tolerance compared to the non-IWS group, that variable did not add to the predictive ability of the multivariable model after adjusting for medication characteristics, such as duration of sedative exposure.

**Discussion**

This study is the largest analysis of risk factors for IWS to date and the first to characterize contextual influences at the system level. In addition to confirming previously observed associations among dose and duration of sedative therapy and
we have provided new evidence for risk factors related to age, pre-existing cognitive impairment and nursing workload. The risk factors identified in this study could inform future practice in sedation management.

Infants under six months of age had the highest risk of experiencing IWS relative to other age groups. Previous studies have either been limited to specific age groups or were underpowered to show an association between age and IWS. Altered pharmacokinetic profiles for sedative medications administered to neonates and infants are related to immature enzymatic pathways. Morphine clearance is lower in infants under six months regardless of hepatic or renal function, resulting in higher serum concentrations and longer half-lives. Midazolam exhibits similar patterns of age-dependent reductions in metabolism. Our results show lower preweaning mean daily doses for both opioids and benzodiazepines among infants under six months, suggesting that adequate sedation was achieved at lower doses. The extended bioavailability of sedative medications in these patients may translate into prolonged receptor occupancy, which has been implicated as a mechanism for tolerance and physical dependence.

Despite the probable physiologic basis for these findings, it is possible that the observed differences in IWS risk based on age are an artifact of the measurement approach: our assessment tool (i.e., the WAT-1) demonstrated age-related variations in IWS symptom presentation during initial validation. Additional research in all age groups with measurement of plasma medication levels and/or clearance is recommended for further exploration.

The etiology of our subjects’ pre-existing cognitive impairment is unknown. There is growing evidence for altered neurotransmitter function in the brains of children
with neurodevelopmental disorders causing cognitive impairments, including aberrant \( \gamma \) -aminobutyric acid (GABA) signaling and differing levels of endogenous opioid production. Prolonged sedative administration may exacerbate existing imbalances in inhibitory and excitatory neurotransmission in these children, with unknown consequences when medication administration ceases. Our data suggest an increased risk for IWS in children with pre-existing cognitive impairment, which may or may not be related to neurochemically-based differences in medication response. The role of pre-existing cognitive impairment is especially challenging to interpret given the frequent exclusion of children with neurologic disorders from studies of IWS. The performance of the WAT-1 in discriminating between symptoms of IWS and behavioral manifestations of cognitive impairment is also relatively unknown, although cognitively impaired children were in the validation sample. As long as sedation management for children with cognitive impairments continues to rely on opioid and benzodiazepine therapy, the potential risk for additional iatrogenic injury in this sub-population requires investigation.

The contribution of severity of illness to patient risk for IWS is still unclear: although neither PRISM III-12 scores nor preweaning number of organ systems in failure were retained as predictors, NEMS scores are calculated from several items related to a patient’s criticality. The PRISM III-12 only captures severity of illness at admission and may not account for changes over the course of the PICU stay, reflected in its poorer performance in predicting mortality for patients with PICU stays over six days. There were too few renal and hepatic failure events for their contribution to IWS to be fully examined. Systemic inflammation and cytokine release associated with critical illness
have been found to decrease cytochrome P450 enzyme activity and midazolam clearance, thereby increasing plasma drug levels and suggesting a possible physiologic explanation for increased risk for IWS among sicker patients. However, the pharmacodynamic effect of these changes is unknown.

Though criticality may have contributed to higher NEMS scores and their association with IWS, the potential effects of nursing workload should also be acknowledged. The use of system-level data makes it impossible to know the frequency or degree to which individual patients with IWS experienced either conditions of greater nursing workload or high nurse staffing ratios. However, higher nursing workload has been associated with more adverse patient outcomes, such as mortality. There may be a critical point at which high nursing workload increases the likelihood of adverse events. In contrast, allocating a greater proportion of nurse staffing to one-to-one patient assignments is generally associated with lower risk of complications. The observed increase in IWS rates with more frequent one-to-one nurse staffing may reflect an ascertainment bias rather than a true effect on IWS risk; units where more nurses spent their entire shift with one patient may have more successfully identified early signs and symptoms of IWS. The observation that units reporting more frequent one-to-one assignments also tended to administer lower cumulative doses of opioids may add support to this hypothesis. That is, with nurses spending more of their time at the bedside, patients were adequately sedated at lower medication doses. These interpretations should be viewed with caution pending prospective exploration with patient-level data.

This model’s predictive performance was lower than expected, but this finding is consistent with results from a previous study testing peak benzodiazepine dose as a risk
factor for IWS (AUC 0.67, 95% CI not reported). A different multivariate predictive model of IWS had better performance (AUC 0.83, 95% CI 0.75-0.92), but neither study corrected for model overfitting and minimal data on validity were provided. Thus, our ability to accurately predict the outcome of IWS based on clinical factors is still unknown, and this study is the first to suggest that system-level variables may also have an effect on IWS outcome. Currently available assessment tools were designed to measure both opioid- and benzodiazepine-related IWS. The maximal sensitivity and specificity of predictive models based on either instrument may be limited by different risk profiles for each phenomenon.

This secondary analysis has limitations. First, WAT-1 assessments were not completed in all patients with ≥5 days of sedative exposure. It is possible that restricting analysis to the subset of patients with WAT-1 scores introduced selection bias, and the results of this analysis are not generalizable to patients with <5 days of sedative exposure. The outcome definition of two WAT-1 scores ≥3 has not been used previously, though it is based on well-established cutoffs. We considered this definition to be a conservative approach to quantifying IWS and reducing potential false positives from unrelated conditions. Subjects with only one WAT-1 ≥3 were assigned to the non-IWS group, but any resulting misclassification would be expected to bias the results toward the null. Finally, while this study identified associations between IWS and several risk factors, it did not provide causal evidence. Additional mechanistic studies are needed. The proposed model should be validated using an independent dataset, particularly for system-level factors collected for individual patients.
In conclusion, IWS is a common complication among pediatric patients recovering from critical illness. We explored the relative contributions of a number of IWS risk factors aside from sedative dose and duration, which offer several avenues for future investigation. Predictive modeling suggests that younger patients and those with pre-existing cognitive impairments are at increased risk for IWS, along with patients who experience higher mean daily opioid doses, longer exposure periods or receive more classes of sedative medications. Inclusion of additional process and system factors provided a novel contribution to the literature. With further prospective validation, the identified risk factors could be used to inform individualized approaches to sedation practice in these critically ill patients, including IWS risk assessments.
Acknowledgments

The authors gratefully acknowledge the work of the RESTORE study investigators, who include: Martha A.Q. Curley (Principal Investigator; School of Nursing and the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Critical Care and Cardiovascular Program, Boston Children’s Hospital, Boston, MA); David Wypij, (Principal Investigator – Data Coordinating Center; Department of Biostatistics, Harvard T.H. Chan School of Public Health; Department of Pediatrics, Harvard Medical School; Department of Cardiology, Boston Children’s Hospital, Boston, MA); Geoffrey L. Allen (Children’s Mercy Hospital, Kansas City, MO); Derek C. Angus (Clinical Research, Investigation, and Systems Modeling of Acute Illness Center, Pittsburgh, PA); Lisa A. Asaro (Department of Cardiology, Boston Children’s Hospital, Boston, MA); Judy A. Ascenzi (The Johns Hopkins Hospital, Baltimore, MD); Scot T. Bateman (University of Massachusetts Memorial Children’s Medical Center, Worcester, MA); Santiago Borasino (Children’s Hospital of Alabama, Birmingham, AL); Cindy Darnell Bowens (Children’s Medical Center of Dallas, Dallas, TX); G. Kris Bysani (Medical City Children’s Hospital, Dallas, TX); Ira M. Cheifetz (Duke Children’s Hospital, Durham, NC); Allison S. Cowl (Connecticut Children’s Medical Center, Hartford, CT); Brenda L. Dodson (Department of Pharmacy, Boston Children’s Hospital, Boston, MA); E. Vincent S. Faustino (Yale-New Haven Children’s Hospital, New Haven, CT); Lori D. Fineman (University of California San Francisco Benioff Children’s Hospital at San Francisco, San Francisco, CA); Heidi R. Flori (University of California at San Francisco Benioff Children’s Hospital at Oakland, Oakland, CA); Linda S. Franck (University of California at San Francisco School of Nursing, San Francisco, CA); Rainer G. Gedeit (Department of
Pediatrics, Medical College of Wisconsin, Milwaukee, WI; Mary Jo C. Grant (Primary Children’s Hospital, Salt Lake City, UT); Andrea L. Harabin (National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD); Catherine Haskins-Kiefer (Florida Hospital for Children, Orlando, FL); James H. Hertzog (Nemours/Alfred I. DuPont Hospital for Children, Wilmington, DE); Larissa Hutchins (The Children’s Hospital of Philadelphia, Philadelphia, PA); Aileen L. Kirby (Oregon Health & Science University Doernbecher Children’s Hospital, Portland, OR); Ruth M. Lebet (School of Nursing, University of Pennsylvania, Philadelphia, PA); Michael A. Matthay (University of California at San Francisco School of Medicine, San Francisco, CA); Gwenn E. McLaughlin (Holtz Children’s Hospital, Jackson Health System, Miami, FL); JoAnne E. Natale (University of California Davis Children’s Hospital, Sacramento, CA); Phineas P. Oren (St. Louis Children’s Hospital, St. Louis, MO); Nagendra Polavarapu (Advocate Children’s Hospital-Oak Lawn, Oak Lawn, IL); James B. Schneider (Cohen Children’s Medical Center of New York, Hyde Park, NY); Adam J. Schwarz (Children’s Hospital of Orange County, Orange, CA); Thomas P. Shanley (C. S. Mott Children’s Hospital at the University of Michigan, Ann Arbor, MI); Shari Simone (University of Maryland Medical Center, Baltimore, MD); Lewis P. Singer (The Children’s Hospital at Montefiore, Bronx, NY); Lauren R. Sorce (Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL); Edward J. Truemper (Children’s Hospital and Medical Center, Omaha, NE); Michele A. Vander Heyden (Children’s Hospital at Dartmouth, Dartmouth, NH); R. Scott Watson (Center for Child Health, Behavior, and Development, Seattle Children’s Research Institute, Seattle, WA); Claire R. Wells (University of Arizona Medical Center, Tucson, AZ).
References


44. Ince I, de Wildt SN, Peeters MYM, Murry DJ, Tibboel D, Danhof M, Knibbe CAJ. Critical illness is a major determinant of midazolam clearance in children aged 1 month to 17 years. *Ther Drug Monit.* 2012;34(4):381-389. doi:10.1097/FTD.0b013e31825a4c3a.


Figures and Tables

Figure 4-1. Mean daily sedation dose preweaning according to age category and IWS status

A. Opioid dose

B. Benzodiazepine dose

Note: Box plots present median (IQR) for each dose by age category, with outlying values (two outliers excluded from mean daily opioid dose preweaning plot)
### Table 4.1. Demographic and clinical characteristics of study sample according to IWS status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IWS (n=544)</th>
<th>Non-IWS (n=613)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at PICU admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) – years</td>
<td>1.1 (0.3-4.4)</td>
<td>1.6 (0.3-6.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>2 weeks to 6 months</td>
<td>207 (38)</td>
<td>197 (32)</td>
<td>0.06</td>
</tr>
<tr>
<td>6 months to 1.99 years</td>
<td>133 (24)</td>
<td>141 (23)</td>
<td></td>
</tr>
<tr>
<td>2.00 to 5.99 years</td>
<td>96 (18)</td>
<td>108 (18)</td>
<td></td>
</tr>
<tr>
<td>6.00 to 17.99 years</td>
<td>108 (20)</td>
<td>167 (27)</td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>239 (44)</td>
<td>282 (46)</td>
<td>0.50</td>
</tr>
<tr>
<td>Non-Hispanic white, n/total n (%)</td>
<td>292/542 (54)</td>
<td>287/607 (47)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cognitive impairment (baseline PCPC &gt;1)</td>
<td>134 (25)</td>
<td>110 (18)</td>
<td>0.003</td>
</tr>
<tr>
<td>Functional impairment (baseline POPC &gt;1)</td>
<td>157 (29)</td>
<td>137 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>PRISM III-12 score</td>
<td>7 (3-12)</td>
<td>6 (3-11)</td>
<td>0.26</td>
</tr>
<tr>
<td>Risk of mortality based on PRISM III-12</td>
<td>3.8 (1.0-11.7)</td>
<td>2.9 (1.0-9.5)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Organ dysfunction preweaning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>259 (48)</td>
<td>273 (45)</td>
<td>0.25</td>
</tr>
<tr>
<td>Neurological</td>
<td>254 (47)</td>
<td>273 (45)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hematological</td>
<td>107 (20)</td>
<td>97 (16)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hepatic</td>
<td>91 (17)</td>
<td>93 (15)</td>
<td>0.44</td>
</tr>
<tr>
<td>Renal</td>
<td>36 (7)</td>
<td>29 (5)</td>
<td>0.17</td>
</tr>
<tr>
<td>No. of failed organ systems preweaning</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Prewearning ECMO support</td>
<td>11 (2)</td>
<td>6 (1)</td>
<td>0.08</td>
</tr>
<tr>
<td>RESTORE intervention</td>
<td>315 (58)</td>
<td>345 (56)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO – extracorporeal membrane oxygenation; IQR – interquartile range; IWS – iatrogenic withdrawal syndrome; PCPC – Pediatric Cerebral Performance Category; PICU – pediatric intensive care unit; POPC – Pediatric Overall Performance Category; PRISM III-12 – Pediatric Risk of Mortality III score from first 12 hours in the PICU

*a Data are median (interquartile range) or number (%) unless otherwise specified

*b PCPC and POPC scores range from 1 to 6, with higher categories indicating greater impairment (Fiser et al., 1992)¹⁸
Table 4-2. Preweaning medication characteristics according to IWS status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IWS (n=544)</th>
<th>Non-IWS (n=613)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary opioid preweaning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>223 (41)</td>
<td>259 (42)</td>
<td>0.68</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>321 (59)</td>
<td>351 (57)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone or remifentanil</td>
<td>0 (0)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary benzodiazepine preweaning</strong></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Midazolam</td>
<td>481 (88)</td>
<td>515 (84)</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>60 (11)</td>
<td>94 (15)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (0.6)</td>
<td>4 (0.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Opioid exposure preweaning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily dose</td>
<td>2.9 (1.8-4.5)</td>
<td>2.6 (1.4-4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak daily dose</td>
<td>4.5 (2.8-7.7)</td>
<td>3.9 (2.2-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>19.1 (11.1-34.1)</td>
<td>15.7 (8.1-26.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Benzodiazepine exposure preweaning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily dose</td>
<td>2.5 (1.4-4.2)</td>
<td>2.1 (1.1-3.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak daily dose</td>
<td>3.8 (2.3-7.1)</td>
<td>3.2 (1.8-6.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>16.0 (8.5-31.5)</td>
<td>12.3 (6.6-25.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>No. days of sedation exposure (opioid and/or benzodiazepine)</strong></td>
<td>6 (5-8)</td>
<td>6 (5-7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tolerance</td>
<td>157 (29)</td>
<td>130 (21)</td>
<td>0.004</td>
</tr>
<tr>
<td>Doubling of Day 2 opioid dose preweaning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of sedative classes received preweaning</td>
<td>3 (2-4)</td>
<td>3 (2-3)</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;3</td>
<td>228 (42)</td>
<td>298 (49)</td>
<td>0.01</td>
</tr>
<tr>
<td>≤3</td>
<td>316 (58)</td>
<td>315 (51)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IWS – iatrogenic withdrawal syndrome

Data are median (interquartile range) or number (%) unless otherwise specified

For group comparisons, continuous opioid and benzodiazepine dose variables were log-transformed to approximately normalize the variables
Table 4-3. System-level characteristics of study sample and associations with site-specific IWS rate

<table>
<thead>
<tr>
<th>Continuous characteristics</th>
<th>Overall&lt;sup&gt;a&lt;/sup&gt; (n = 31)</th>
<th>Correlation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICU beds</td>
<td>22 (16-29)</td>
<td>-0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean daily census</td>
<td>15 (11-19)</td>
<td>-0.05</td>
<td>0.81</td>
</tr>
<tr>
<td>Annual admissions</td>
<td>1116 (792-1827)</td>
<td>0.07</td>
<td>0.70</td>
</tr>
<tr>
<td>No. PICU attending physicians</td>
<td>9 (7-10)</td>
<td>-0.10</td>
<td>0.59</td>
</tr>
<tr>
<td>No. PICU nurses</td>
<td>69 (47-97)</td>
<td>0.04</td>
<td>0.82</td>
</tr>
<tr>
<td>Percent staffing that is 1 nurse:1 patient</td>
<td>30 (20-50)</td>
<td>0.34</td>
<td>0.06</td>
</tr>
<tr>
<td>Percent with BSN&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80 (74-90)</td>
<td>-0.27</td>
<td>0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binary characteristics</th>
<th>Sites with characteristic</th>
<th>Sites without characteristic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical management: Open PICU</td>
<td>20 49 (3)</td>
<td>11 42 (4)</td>
<td>0.26</td>
</tr>
<tr>
<td>ANCC Magnet Recognition®</td>
<td>15 45 (3)</td>
<td>16 49 (4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Professional advancement program for nurses</td>
<td>24 46 (3)</td>
<td>7 51 (7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Unit-based pharmacist participates in rounds</td>
<td>26 48 (3)</td>
<td>5 40 (11)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Abbreviations: ANCC – American Nurses Credentialing Center; BSN – Bachelor’s of Science in Nursing; IQR – interquartile range; IWS – iatrogenic withdrawal syndrome; PICU – pediatric intensive care unit; SBS – State Behavior Scale

<sup>a</sup>Reported values are median (IQR)

<sup>b</sup>Pearson’s correlations were calculated using analytic weights based on the inverse variance of the rate of IWS by site for continuous predictors

<sup>c</sup>Calculated correlation based on data from 29 sites

<sup>d</sup>Reported values are mean (SE) proportion of subjects with IWS weighted by the inverse variance of the rate of IWS by site
Table 4-4. Predictive models of IWS

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Variables collected by subject only</th>
<th>Variables collected by subject and by PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted ORs (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Patient-level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks to 6 months</td>
<td>2.63 (1.65-4.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months to 1.99 years</td>
<td>1.62 (1.08-2.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>2.00 to 5.99 years</td>
<td>1.32 (0.89-1.96)</td>
<td>0.16</td>
</tr>
<tr>
<td>6.00 to 17.99 years</td>
<td>Ref</td>
<td>--</td>
</tr>
<tr>
<td>Cognitive impairment (baseline PCPC &gt;1)</td>
<td>1.87 (1.34-2.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of sedative exposure preweaning</td>
<td>1.07 (1.01-1.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean daily opioid dose preweaning(^a)</td>
<td>1.25 (1.00-1.57)</td>
<td>0.053</td>
</tr>
<tr>
<td><strong>Process-level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of preweaning sedative classes ≥ 3</td>
<td>1.34 (1.01-1.79)</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>System-level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median preweaning NEMS score(^b)</td>
<td>1.62 (1.12-2.34)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pct. of staffing 1 RN: 1 patient(^c)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Abbreviations: NEMS – Nine Equivalents of nursing Manpower use Score; OR – odds ratio; PCPC – Pediatric Cerebral Performance Category; RN – registered nurse
\(^a\) Odds ratio reported for change from 25\(^{th}\) to 75\(^{th}\) percentile of log-transformed mean daily opioid dose
\(^b\) Odds ratio reported for a 10-unit change in NEMS score
\(^c\) Odds ratio reported for a 10% change in value
Patient, process and system predictors of iatrogenic withdrawal syndrome in critically ill children

Kaitlin M. Best, PhD(c), MS, RN
David Wypij, PhD
Lisa A. Asaro, MS
Martha A. Q. Curley, PhD, RN, FAAN

Online Data Supplement
Supplemental Methods

Variables and measures: Medication data included cumulative, mean, and peak daily opioid dosage (in morphine equivalents per kg of body weight), cumulative, mean, and peak daily benzodiazepine dosage (in midazolam equivalents per kg of body weight), and administration of any other sedative medications (e.g., chloral hydrate, clonidine, dexmedetomidine, ketamine, pentobarbital, phenobarbital, and propofol), all collected to the start of opioid weaning. Daily and cumulative sedative medication doses were compared using standard equivalencies.\(^1\) Specifically, morphine equivalent conversion factors to equal 1 mg morphine sulfate were as follows: 15 µg remifentanil; 15 µg fentanyl; 0.15 mg hydromorphone; and 0.3 mg methadone. Midazolam equivalent conversion factors to equal 1 mg midazolam were: 0.2 mg clonazepam; 0.3 mg lorazepam; and 2 mg diazepam. A composite variable for duration of sedation was created, reflecting days where either opioids or benzodiazepines were administered in the preweaning period. The start of opioid weaning was reported by the clinician and verified or reassigned according to a standard algorithm. Tolerance to opioids was defined as a doubling of the Day 2 opioid dose prior to the start of weaning. An inconsistent pattern of weaning was assigned to subjects with a course of weaning that included ≥20% increases in total daily opioid doses at any time after the start of opioid weaning.

Patient-level demographic and clinical data included age, gender, race/ethnicity, severity of illness and mortality risk (Pediatric Risk of Mortality (PRISM) III-12),\(^2\) and need for ECMO in the preweaning period. Subjects were considered to have a pre-existing cognitive or functional impairment if their Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC)\(^3\) scores were >1,
respectively. Each subject was evaluated for the presence of acute organ dysfunction prior to the start of opioid weaning based on daily lab values and other clinical data. All RESTORE subjects had respiratory dysfunction. The number of organ systems in failure was summed for the preweaning period.

Process-level variables included RESTORE group assignment and the number of sedative medication classes administered (i.e., opioid, benzodiazepine, alpha-2-agonist, ketamine, barbiturate, propofol, and chloral hydrate). Compliance with sedation assessments during the pre-weaning period was a continuous variable based on daily assessment of a child’s level of sedation using the State Behavior Scale. This analysis averaged daily compliance over the preweaning period, yielding a percent compliance for each subject.

Items drawn from the pre-randomization organizational assessments included: hospital accreditation status with the American Nurses Credentialing Center (i.e., Magnet Recognition® status) and availability of a professional advancement program for nurses; PICU characteristics, such as unit-type (i.e., open versus closed), bed capacity, budgeted census, and number of admissions in the preceding year; and staffing characteristics, such as number of attending physicians, fellows, and registered nurses, and typical nurse-to-patient ratios.

**Power calculation:** A total of 34 potential predictors variables at the patient-, process- and system-level were identified for evaluation in this secondary analysis (Table E1). Therefore, approximately 340 events were needed. Assuming an incidence rate of approximately 30% for IWS in the study population, logistic regression of the binary response variable (i.e., IWS versus no IWS) on continuous, normally distributed
explanatory variables with an inflated sample size of approximately 1160 observations was found to achieve 80% power at a 0.05 significance level to detect an odds ratio of 1.7. The estimated sample size was inflated to account for intra-cluster correlations due to the cluster-randomized design of the parent study. Sample size calculations were based on a small effect size ($R^2 = 0.08$) from previous studies to produce conservative estimates, and it was anticipated that the study would be adequately powered even if some patients were excluded.

**Model diagnostics:** Preliminary model building was completed, and automated stepwise regression with bootstrapping was used to check manual variable selection. Related models were compared using Aikake information criterion (AIC) and sample-size corrected Bayesian information criterion (BIC) values. These analyses were completed using Mplus version 7 (Muthén & Muthén, Los Angeles, CA). After determining the final model, model assumptions and fit were checked using $c$-statistics, receiver operating characteristic (ROC) and calibration curves. The robustness of the findings was further assessed using $k$-fold cross-validation for model calibration and bootstrapping procedures to obtain bias-adjusted confidence intervals.
### Supplemental Table

Table 4-5. Predictor variables of interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
<th>Timing of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>Admission value by subject</td>
</tr>
<tr>
<td>Gender</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Binary [Non-Hispanic White/ Minority]</td>
<td></td>
</tr>
<tr>
<td>Pre-existing cognitive disability</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Pre-existing physical disability</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Severity of illness (PRISM III-12 score)</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Meets organ dysfunction criteria</td>
<td>Categorical</td>
<td>Preweaning summary by subject</td>
</tr>
<tr>
<td>Extracorporeal support required during hospitalization preweaning</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Tolerance to opioids</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Peak, total and cumulative [preweaning] opioid exposure and duration</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Peak, total and cumulative [preweaning] benzodiazepine exposure and duration</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td><strong>Process-Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of classes of sedative agents</td>
<td>Categorical</td>
<td>Preweaning summary by subject</td>
</tr>
<tr>
<td>Sedation assessment compliance</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Inconsistent pattern of weaning</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>RESTORE intervention</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td><strong>System-Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing workload (NEMS score)</td>
<td>Continuous</td>
<td>Preweaning summary by subject</td>
</tr>
<tr>
<td>Unit-based pharmacist participation in daily rounds</td>
<td>Binary</td>
<td>By PICU</td>
</tr>
<tr>
<td>Total number of PICU beds</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Mean PICU daily census</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Annual PICU admissions</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Number of PICU attending physicians</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Number of PICU nurses</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Proportion of staffing with 1 nurse:1 patient</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Proportion of BSN-prepared nurses</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Professional advancement program for nurses</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>ANCC Magnet Recognition</td>
<td>Binary</td>
<td></td>
</tr>
<tr>
<td>Medical management: Open PICU</td>
<td>Binary</td>
<td></td>
</tr>
</tbody>
</table>


CHAPTER 5
DISCUSSION AND CONCLUSION

Sedation management in the pediatric intensive care unit (PICU) is a complex process that requires the consideration of many factors to proceed optimally; there are multiple decision points that could potentially set a patient on the path to experiencing iatrogenic withdrawal syndrome (IWS). Sedative medications elicit variable patient responses, so patients are prescribed medications at pharmacokinetically and pharmacodynamically appropriate doses to achieve the desired effects (Johnson et al., 2012). Clinical practice has gradually incorporated routine evaluation of pain and level of sedation (Playfor et al., 2006), which has improved patient comfort during the critical phase of illness. To a lesser extent, clinicians are increasingly aware of the potential for medication tolerance, which is typically addressed by increasing sedative doses to maintain therapeutic effectiveness (Anand et al., 2010). This careful focus on patient comfort must be balanced against other clinical priorities during recovery, such as endotracheal extubation. The point at which concurrent ventilator and sedation weaning begins generates conflicting goals of preventing respiratory depression and promoting spontaneous breathing while avoiding patient discomfort (Brinker, 2004). Optimal sedation arguably requires a smooth transition from acute illness to recovery, especially when poorly executed sedation weaning leads to uncomfortable complications, like IWS, which are profoundly distressing for patients and families. Unfortunately, little attention has been paid to characterization of the crucial period of sedative weaning and the events that follow. This dissertation study contributed to current knowledge regarding pediatric
sedation management by exploring the relationship between weaning and IWS outcomes, and by identifying additional contributors to the development of IWS.

Summary and Overall Goals

The three papers presented in this dissertation study collectively accomplished the following objectives: 1) exploring the available literature on iatrogenic withdrawal syndrome (IWS) to identify known and hypothesized risk factors for IWS in pediatric patients recovering from critical illness, 2) generating and characterizing patterns of sedation weaning to examine their association with the outcome of IWS, and 3) constructing a predictive model of patient risk for IWS to suggest improvements in future care of patients being weaned from sedation. The conceptual model created in the first paper (Chapter 2) elucidated relationships that were further explored in the remaining analyses (Chapters 3 and 4) and provided a framework for interpreting their findings. For example, tolerance and weaning were two identified concepts that were intricately related to IWS but which required more empirical evaluation. The description of usual clinical practice for sedative weaning in drug tolerant children (Chapter 3) tested operational definitions that performed well, warranting their inclusion in the exploratory modeling of IWS risk completed in Chapter 4.

Major Findings: Tolerance

Physiologically, tolerance is an adaptive process whereby changes in receptor number and composition, uncoupling of secondary messenger systems, and increased release of various neuroactive substances are hypothesized to cause decreased therapeutic effectiveness of medications (Anand et al., 2010; Barr et al., 2011; Vinkers & Olivier,
Tolerance is neither necessary nor sufficient for the development of physical dependence and subsequent IWS (Vinkers & Olivier, 2012), although tolerance and IWS may share certain predisposing factors, including sedative duration. They are distinct phenomena that occur during and after treatment, respectively, and have different implications for clinical management. Tolerance is undesirable since it interferes with the attainment of optimal sedation, and investigations of predictors for tolerance (Anand et al., 2013) may be valuable for increasing the efficiency of sedation practice. When managed through appropriate dose escalation in acute illness and gradual weaning during recovery, tolerance is not directly harmful to patients. It is only when tolerance leads to physical dependence and subsequent IWS that added patient discomfort, anxiety for families, and increased costs of care manifest (Franck et al., 1998; Johnson et al., 2012; Sorce, 2005). Thus, for the purposes of this investigation of risk factors for IWS, tolerance is only relevant in the subpopulation of patients for whom it develops prior to IWS.

Unfortunately, quantifying tolerance remains challenging. Since the exact cellular mechanisms underlying medication tolerance are still under investigation, there are no biological markers signaling its development. Providers have traditionally relied on dose escalation and decreased effectiveness of sedative medications as clinical indicators of tolerance (Anand et al., 2010). Opioid dose escalation is not specific to tolerance, as it could be related to the increased need for post-surgical analgesia or sub-optimal initial doses. The revised operational definition of tolerance that was used in the second and third papers accounted for this lack of specificity by comparing later opioid doses to the Day 2 dose, rather than the first 24 hours’ dose as in previous publications (Anand et al.,
2013). Yet over 20% of subjects without IWS (based on WAT-1 scores) still met criteria for tolerance in both studies, further illustrating that tolerance may be insufficient to trigger physical dependence and IWS in the absence of other risk factors. This result may also be indicative of a continued lack of specificity in the revised definition of tolerance. More accurate clinically-based definitions of tolerance require a subjective assessment of the point at which adequate sedation was achieved in order to determine when therapeutic effectiveness starts to diminish, which may not be feasible for patients along varying illness trajectories and which poses problems for generalizability and reproducibility. These are all important considerations that may help explain why tolerance was not retained as a significant predictor in the final multivariable model of IWS risk.

In the conceptual model from Chapter 2, the various risk factors for IWS were classified as either tolerance- or non-tolerance-related. From a theoretical standpoint, it is still reasonable to consider tolerance as a potential contributor to IWS risk for certain patients, since tolerant patients appear to experience longer durations of sedative exposure. Alternatively, evaluating the sub-population of patients who develop tolerance but not physical dependence may prove to be advantageous, if protective factors could be identified that prevent the development of IWS. In either case, further work in this area may need to wait for more precise measures of tolerance to be developed, separating it from the other clinical influences driving dose escalation in the context of critical illness.

Major Findings: Weaning

Sedative weaning has received limited attention in the pediatric literature, except in studies testing the use of pharmacologic therapies to facilitate faster weaning without precipitating IWS (Bowens et al., 2011; Jeffries, McGloin, Pitfield, & Carr, 2012;
Johnson et al., 2010; Meyer & Berens, 2001; Siddappa et al., 2003; Tobias, 2006). To date, published reports on sedation weaning have relied on quantifying dose reductions as percentages of the original dose (Ducharme et al., 2005), often assuming that weaning occurs as a linear decrease in dose over time at a rate determined by the healthcare provider. Only one recent descriptive study described daily opioid tapering that included increases in dose after the start of weaning, which occurred in 88% (n=22) of patients (Fisher et al., 2013). The portion of this dissertation study investigating patterns of weaning demonstrated that nearly half of patients experienced inconsistent patterns of weaning, which were associated with lower average percent drops in opioid dose and a higher incidence of IWS. Both prospective studies described in this dissertation further showed that the rate of dose reduction is not a key determinant of either weaning trajectory or development of IWS.

It was somewhat unexpected that predictors of inconsistent weaning patterns could not be identified from preweaning variables. However, on further scrutiny this difference in findings between the second and third papers – that is, that clinical variables may predict the outcome of IWS but not weaning patterns – highlights the fact that the etiology of IWS risk is multifactorial. These results also suggest that variations in sedative weaning are better explained by clinician or system factors than by inherent differences in severity of illness or sedative responsiveness in individual patients. Although additional work should prospectively examine this hypothesis, if confirmed it reinforces the need to critically reexamine the process in which sedation-related decisions are made in the PICU.
Major Findings: Patient-Level Risk Factors

The systematic review (Chapter 2) identified an area of disagreement in the current literature on patient-level risk factors for IWS: the evidence was inconsistent regarding the contribution of age to IWS risk, with some studies suggesting associations with either younger or older age. The results described in Chapter 4 provide evidence to resolve this question, since younger children had the highest incidence of IWS of the four age groups examined. The high rate of IWS in young infants was primarily interpreted in the context of developmental changes in the pharmacokinetics of sedative drugs; namely, that the CYP3A4 and UGT2B7 enzymes are differentially expressed and have low activity during the first days to weeks of life (de Wildt, de Hoog, Vinks, van der Giesen, & van den Anker, 2003; Knibbe et al., 2009; McRorie, Lynn, Nespeca, Opheim, & Slattery, 1992; Salem, Johnson, Abduljalil, Tucker, & Rostami-Hodjegan, 2014). Rates of drug metabolism and clearance change from birth to 6 or 12 months (Anderson & Larsson, 2011; Knibbe et al., 2009), depending on the individual patient’s physiology and the medication under examination (Kearns et al., 2003).

The lower mean daily opioid and benzodiazepine doses observed in patients under six months suggest that the ontogeny of drug metabolism in these patients was taken into account in dosing during the preweaning period. Since receiving lower doses of sedative medications still did not result in a lower incidence of IWS in this patient group, perhaps a greater awareness among clinicians of the potential effects of delayed clearance on the development of physical dependence is warranted. Specifically, daily dose reductions (Anand et al., 2010; Galinkin & Koh, 2014) may be misaligned with extended hepatic clearance times in young infants, resulting in dramatic changes in plasma serum
concentrations during weaning. More gradual weaning may be necessary in the youngest group of patients to prevent the development of IWS. There were no age-related differences in the patterns of weaning described in Chapter 3, which could mean that signs of IWS are not addressed with rescue medications as often in young infants. A simpler explanation is that young infants are weaned in a similar manner to older patients, suggesting an opportunity both to try more individualized sedation or weaning approaches in infants under six months and to improve the management of IWS symptoms as they occur in these patients.

Although the literature review identified several anecdotal reports of more frequent IWS in children with pre-existing disorders or hypoxemic brain injuries, it was surprising that the study in Chapter 4 was able to show a relationship between pre-existing cognitive impairment and IWS. The Pediatric Cerebral Performance Category (PCPC) is a gross measure of cognitive impairment in children, which has been correlated with risk of mortality, PICU length of stay, discharge care needs and long-term developmental outcomes (Fiser et al., 2000; Fiser, 1992). However, PCPC scores have not been previously used to predict more short-term outcomes or complications that are contingent upon several aspects of clinical care. In the case of IWS, pre-existing cognitive impairment as a risk factor for IWS may be too granular to drive real changes in sedation management without further investigation. As described in Chapter 4, neurochemical differences in excitatory and inhibitory transmission may explain this finding, but additional pre-clinical work is needed to explore the pharmacodynamics of sedative medication activity in neurologically impaired brains.
As a general observation, the use of sedative medications in children with cognitive and neurological impairments is relatively poorly characterized. For example, only recently have studies been published to counter the notion that children with Down’s syndrome have higher opioid requirements than other critically ill children (Valkenburg et al., 2012; Van Driest et al., 2013). This gap in the literature is problematic, given that up to a quarter of PICU patients may have pre-existing cognitive impairments (Graham, Dumas, O’Brien, & Burns, 2004) and that advances in medical care have led to increasing numbers of children with technological dependence and/or chronic conditions with neurologic components (Namachivayam et al., 2010; Odetola, Gebremariam, & Davis, 2010). Up to this point, evidence has shown that sedative medications are effective for use in children with cognitive impairments (Buck & Willson, 2008; Kilbaugh, Friess, Raghupathi, & Huh, 2010; Valkenburg, van Dijk, de Klein, van den Anker, & Tibboel, 2010), but the results of this study suggest that more careful evaluation of the safety and long-term effects of these medications may be needed in this population.

There is a robust body of evidence for sedative dose and duration as risk factors for IWS (Chapter 2). The results of this dissertation unanimously confirmed the importance of considering both variables in evaluating a patient’s probable course of weaning and predicting risk for IWS; therefore, the inclusion of both a dose and duration variable in the predictive model (Chapter 4) gives some measure of face validity to the findings. In addition, though it is intuitive for clinicians that patients receiving higher preweaning doses and/or longer durations of sedation have more difficulty with weaning, the analysis presented in Chapter 3 was the first direct evaluation of the contributions of preweaning sedative dose and duration to weaning outcomes. A problem in some older
studies of IWS (Bergman et al., 1991; Dominguez et al., 2003; Fonsmark et al., 1999; Franck et al., 1998; French & Nocera, 1994; Hughes et al., 1994; Katz et al., 1994) that was identified and addressed in these dissertation studies, is the inclusion of medication doses received after the start of weaning in quantifying the relationship between sedative exposure and IWS. A few recent investigations have differentiated between pre- and post-weaning doses and acknowledged the correlations among medication variables (Franck et al., 2008; Franck et al., 2012). However, by highlighting this gap in previous approaches, these methods and findings add a much-needed level of conceptual clarity to the study of contributors to IWS in critically ill children.

Major Findings: Process-Level Risk Factors

The only process-level factor found to be a significant predictor of IWS was number of sedative agents used in the preweaning period: subjects who received three or more classes of sedative medications were more likely to experience IWS. The same variable did not achieve statistical significance in the study of weaning patterns, though inconsistently weaned patients did appear to receive more sedative agents in the preweaning period, and receipt of additional sedative classes occurred more frequently among inconsistently weaned patients during weaning (p<0.001). Taken together, these findings highlight the difficulty of interpreting the relationship between multi-drug therapy and IWS: prescription of additional sedative medications during weaning is most indicative of attempts to manage emergent signs and symptoms of IWS, but in the preweaning period the clinical rationale for this approach requires some speculation. It is likely that at least some of the children who received three or more sedative agents were difficult to sedate with traditional opioid and benzodiazepine medications. There is an
incomplete understanding of the reasons for pharmacodynamic variation in sedative response in critically ill children (Johnson et al., 2012; Vet, de Hoog, Tibboel, & de Wildt, 2011), and even less about how it might translate into a predisposition for physical dependence or difficulties with weaning. This finding is particularly perplexing to explain given that the direction of effect was opposite that in a previously published model of IWS risk (Ista et al., 2013), which reported seemingly protective effects for one or two additional sedative medications (respectively, OR 0.11, 95% CI 0.28-0.42, p=0.001; OR 0.19, 95% CI 0.05-0.76, p=0.02). However, that study did not clearly describe whether additional sedatives were administered solely in the preweaning phase and did not distinguish between medications treating signs and symptoms of withdrawal (i.e., clonidine, ketamine, fentanyl) versus other sedatives (i.e., propofol). Their findings may reflect more proactive treatment of mild symptoms of IWS during weaning, while ours specifically address sedative needs in the preweaning period.

It is interesting that RESTORE group assignment did not appear to influence the outcome of IWS. The primary study found that patients in the intervention group had fewer days of opioid exposure, received fewer sedative classes (including less methadone), and, based on sedation assessments, were more often considered to be awake and calm during mechanical ventilation than subjects in the control group (Curley et al., 2015). Nevertheless, IWS rates reported in the primary paper were 68% in both study groups. This result may be a reflection of the complex nature of IWS, wherein other determinants of a patient’s risk could offset the beneficial effects of lower medication doses. For example, more patients less than two years of age were enrolled in the intervention group, and their higher observed rates of IWS might have obscured the
potentially preventive effects of the sedation protocol on the incidence of IWS. Compliance with WAT-1 assessments was also higher in the intervention group, raising the distinct possibility that IWS was more likely to be identified in those patients. Thus, the results in Chapter 4 cannot be interpreted as a statement on the effectiveness of standardized sedation protocols in preventing IWS, and it is recommended that additional studies using IWS as the primary outcome be developed to more thoroughly evaluate this relationship.

Major Findings: System-Level Risk Factors

A novel contribution of this dissertation was the evaluation of the effects of the healthcare system on the outcome of IWS. As a phenomenon defined primarily by its clinical signs and symptoms, IWS is typically described at the patient level. Many previous investigations have been limited to single centers and could not comment on variations across sites. However, certain authors noted process challenges (Carnevale & Ducharme, 1997; Ducharme et al., 2005; Jin et al., 2007) which suggested elements of sedation management that were common across institutions. The literature review (Chapter 2) demonstrated that studies of IWS up to this point have frequently lacked contextualization based on the unique circumstances in which sedation occurs, namely, within complex health systems.

Systems factors were not directly evaluated in the second study, but using baseline data from the RESTORE trial yielded findings that were potentially driven by practice norms at each of the participating PICUs. Unmeasured influences on inconsistent weaning may have existed, such as periods of high unit census and hospital policies prohibiting use of continuous infusions on general floor units (Tobias, 2000). Clinicians
sometimes perceive that gradual tapering of sedatives will delay extubation or discharge from the PICU to the floor (Tobias, 1996, 1999), despite the fact that studies of standardized sedation protocols including weaning (Deeter et al., 2011; Jin et al., 2007; Keogh, Long, & Horn, 2015) have shown decreased or unchanged lengths of stay. However, there have been no systematic investigations of the precise relationship between sedative weaning as the primary intervention and time to extubation or discharge, besides a study showing no difference in the success rate of methadone-facilitated weaning using a 5 or 10 day protocol (Bowens et al., 2011). Nevertheless, over the course of the RESTORE trial, clinicians expressed a declining inclination to wean sedative medications (Best, Wypij, & Curley, 2014), presumably in favor of rapid discontinuation of continuous infusions. Thus, if faced with a shortage of PICU beds and external pressure to move patients to the floor, patients who otherwise would be weaned more slowly might be pushed into the process prematurely. This explanation is purely speculative, and may be countered by the observation that percent decreases in opioid dose were lower among inconsistently weaned patients.

In the final paper, both high nursing workload and greater proportions of high nurse to patient staffing ratios were identified as contributors to IWS risk. The discussion in Chapter 4 thoroughly explored the potential implications of these findings, which unfortunately offer limited room for interpretation because of the lack of patient-level data. Nurse to patient staffing ratios are often used in health policy research as an indirect indicator of nursing workload (Carayon & Gürses, 2005; Cimiotti, Barton, Chavanu Gorman, Sloane, & Aiken, 2014; Tubbs-Cooley et al., 2013), and higher levels of nurse staffing are typically associated with improved quality of care and better patient
outcomes (Numata et al., 2006). Therefore, the direction of the effect of staffing ratios on IWS incidence contradicted the finding that higher nursing workload (based on NEMS scores) was a risk factor for IWS. Although the most logical explanation is an effect of ascertainment bias, there may be other relevant but unmeasured influences at sites with higher proportions of one-to-one nurse staffing that do exert a true effect on increased risk for IWS, such as work environment (Kelly, Kutney-Lee, Lake, & Aiken, 2013; McHugh et al., 2013) or nursing education (Aiken et al., 2003; Egerod, 2002; Guttormson et al., 2010; Kutney-Lee et al., 2013).

The fact that unit size and number of annual admissions were not found to have significant relationships with IWS is not unusual. One systematic review of organizational research in healthcare reported that more than 45% of studies investigating the effects of the system or structure on patient outcomes yielded non-significant findings (Hearld et al., 2008). This observation stems in part from the complexity of clinical patient care, especially in the PICU, where a diverse set of process and system influences can operate to varying degrees to either directly or indirectly influence patient-level outcomes. However, previous pediatric studies have demonstrated associations between PICU volume and patient outcomes (Tilford, Simpson, Green, Lensing, & Fiser, 2000). The final study (Chapter 4) attempted to address this challenge by adjusting for factors at the patient, process and system levels. It is also possible that the reported proportion of high nurse-to-patient staffing ratios at each site was indirectly related to unit volume or census, and therefore including the staffing variable accounted for those effects. Overall, a few system-level variables did reach statistical significance in this analysis. Further
exploration of systems influences on IWS might confirm these results or identify additional system-level contributors.

Limitations

The limitations of this dissertation include the use of an unvalidated conceptual model, difficulty in operationally defining and measuring certain variables of interest, and potential biases in the available study sample. The conceptual model developed in the first study was derived through a qualitative synthesis of the available literature on IWS risk; it is possible that another author provided with the same data might have reached different conclusions. The remaining studies in this dissertation used this framework to guide variable selection, which may have led to erroneous assumptions about the relationships between variables. However, the final study successfully identified predictor variables at each level of the model, lending some support to the initial hypothesis that influences outside of the patient ought to be considered.

As in previous studies of sedation management in the PICU, these analyses were unable to differentiate between the effects of opioid and benzodiazepine exposure on either weaning patterns or IWS risk. Only two studies to date have examined both opioid and benzodiazepine patterns of weaning together (Ducharme et al., 2005; Ista et al., 2013), in part due to the difficulty of defining the start of weaning for each individual medication. Rather than replicating these approaches, this dissertation defined the start of weaning relative to opioid administration, which has been more thoroughly described as a contributor to IWS in children recovering from critical illness. This design decision may have neglected important information that could have been gleaned from considering
both medications together, especially since less is known about physical dependence on benzodiazepines and appropriate weaning approaches.

Inconsistent patterns of weaning were more frequently observed among patients with IWS compared to non-IWS patients, but ultimately this association was not explored further in the final study (Chapter 4), in part because of the difficulty in demonstrating causal relationships in this study design. Specifically, inconsistent weaning could not be definitively identified as the cause of higher observed WAT-1 scores in either of the studies including weaning pattern. Future prospective analyses could investigate the timing of onset of IWS symptoms relative to the start of inconsistent weaning.

Compliance with standardized assessments was less than perfect in the studies that relied upon baseline (Chapter 3) and post-randomization data (Chapter 4), making interpretation of the results more challenging. Difficulties with compliance have been frequently reported in the literature on sedation assessment: a recent survey noted that although 70% of respondents worked in PICUs implementing standardized sedation assessment tools, only 42% of clinicians actually used them to guide sedation management (Kudchadkar, Yaster, & Punjabi, 2014). Given the recent development of both the WAT-1 (Franck et al., 2008; Franck et al., 2012) and its Dutch counterpart, the SOS (Ista et al., 2008; Ista et al., 2013), very little research has evaluated compliance with withdrawal assessment, particularly over the course of a five year clinical trial. However, published findings indicate inconsistent use in clinical practice (Jeffries et al., 2012; Keogh et al., 2015). It is likely that non-compliance with sedation and withdrawal assessments is at least in part related to clinician biases: patients who were perceived to have a “smoother” sedation course may have been less likely to be assessed, if they were
considered by clinicians to be at lower risk for IWS than patients with more complex sedation needs. However, there was no way to directly evaluate the effects of clinician attitudes and beliefs in the context of this secondary analysis.

Finally, as has been stated previously, the association between system-level variables and IWS outcome could not be adequately assessed in the absence of individually collected data for each subject. As a secondary analysis, the self-reported site-level organizational assessment data were the only available system-level variables. There was variation over the course of the study in terms of what data was available at each site, and many sites simply did not have processes in place for obtaining the requested data, particularly for nursing variables. As a result, there was more missing data in the organizational dataset than in the larger study.

Future Directions

The most obvious contribution of this dissertation work is to suggest additional caution in the approach to sedation management and weaning in certain groups of critically ill children. Patients under six months of age may require an alternative strategy of sedation titration to avoid doses that induce physical dependence and possibly different weaning approaches to avert symptoms of IWS. However, weaning alone may be ineffective as an approach to preventing IWS. Sedation in children with pre-existing cognitive impairments should also be managed conservatively. The design of this dissertation study precludes any mechanistic explanation for why these patients may have experienced more IWS despite similar sedative doses and duration of exposure. It is reasonable to hypothesize that these patients have altered responses to sedative
medications due to pre-existing neurochemical differences, but additional pre-clinical and clinical studies are needed.

Although this study was originally intended to investigate the relationship between race/ethnicity and risk for IWS, this was not done for several practical reasons. Documentation of race/ethnicity in the RESTORE trial was based upon the research personnel’s impressions of the patient on admission and was not self-reported, raising concerns about potential misclassification. The theoretical basis for including race/ethnicity as a potential risk factor for IWS could not be substantiated; it is unknown whether the underlying distribution of polymorphisms in genes responsible for opioid and/or benzodiazepine metabolism would be reproduced by the available codings of race/ethnicity without analysis of biological data from the sampled RESTORE subjects. Adopting race/ethnicity as proxies for genetic differences in drug metabolism is no longer a recommended approach in pharmacogenetic research (Lee, 2009). Therefore, future studies including patient genotypes for potentially contributory genes – such as single nucleotide polymorphisms in the mu opioid receptor (OPRM1), ATP binding cassette transporters (ABCB1), and the cytochrome P450 family (Anand et al., 2010) – should examine direct relationships with the outcome of IWS. Some of this work is already in progress, with promising results (Beer et al., 2013).

This study of risk factors for IWS in pediatric patients recovering from critical illness has provided valuable insights into current processes of sedation management in the PICU, but it also raises a host of new questions. For example, despite efforts to explore the system context of sedation management in the PICU, little is known about the physical environment in which the children in these analyses were receiving sedation.
therapy and recovering from critical illness. Although gradual weaning remains the most promising approach to reducing the incidence of IWS, there is increasing interest in reducing noxious environmental stimuli as a means to decreasing sedative needs in critically ill children. Families could be engaged in helping to use non-pharmacologic measures for reducing agitation, such as music therapy, massage, and other complementary therapies (Brinker, 2004; Stephen Playfor et al., 2006). However, the success of such interventions is contingent upon the unique organizational dynamics of the PICU (Burns, 2012; Thomas & Dhanani, 2010).

If the system-level variables identified in this study are examined prospectively with patient-level data and similar relationships are observed, it may be advisable to examine strategies for increasing resources and better allocating nursing assignments for high-risk patients. Recent studies have suggested that inadequate nursing resources are associated with reduced surveillance for potential changes in patient condition (Cimiotti et al., 2014) and more instances of “missed care” (Ball, Murrells, Rafferty, Morrow, & Griffiths, 2014). It would be interesting to probe the process of how nurses allocate their time to sedation-related versus other care activities, how sedation assessment and weaning are prioritized, and what additional resources could help support optimal practice, thereby reducing nursing workload. Such an investigation could incorporate an assessment of the quality of interprofessional dialogue surrounding sedation; relying on Magnet status as an indicator of the quality of work environments may have been too granular an approach in this study, and previous findings strongly suggest that interprofessional communication regarding sedation goals influences nurses’ attitudes toward weaning and IWS assessment (Suddaby & Josephson, 2013).
Conclusion

This dissertation has explored and advanced knowledge regarding iatrogenic withdrawal syndrome in children recovering from critical illness and weaning from sedative medications. The conceptual model proposed in the first paper provided a framework for designing and interpreting the remaining two studies, although external validation is needed. In addition to critically examining the role of tolerance in precipitating IWS, this dissertation has elucidated the relationship between weaning and IWS, and provided a reproducible methodology to guide future research. Most importantly, both classic and novel risk factors together contributed to a predictive model of IWS risk that adjusted for variables at the levels of the patient, process and system.
APPENDICES

Appendix 1. Withdrawal Assessment Tool-version 1 (WAT-1)

<table>
<thead>
<tr>
<th>Patient Identifier</th>
<th>Date:</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information from patient record, previous 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any loose watery stools</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>Any vomiting/wretching/gagging</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>Temperature &gt; 37.8°C</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>2 minute pre-stimulus observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>SBS ≤ 0 or asleep/awake/calm = 0</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>None/mild = 0</td>
<td></td>
</tr>
<tr>
<td>Any sweating</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>Uncoordinated/repetitive movement</td>
<td>None/mild = 0</td>
<td></td>
</tr>
<tr>
<td>Yawning or sneezing</td>
<td>None or 0 0.02 1</td>
<td></td>
</tr>
<tr>
<td>1 minute stimulus observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle to touch</td>
<td>None/mild = 0</td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal = 0</td>
<td></td>
</tr>
<tr>
<td>Post-stimulus recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to gain calm state (SBS ≤ 0)</td>
<td>&lt; 2 min = 0</td>
<td></td>
</tr>
<tr>
<td>Total Score (0-12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WITHDRAWAL ASSESSMENT TOOL (WAT – 1) INSTRUCTIONS**

- Start WAT-1 scoring from the first day of weaning in patients who have received opioids &/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days). Continue twice daily scoring until 72 hours after the last dose.
- The Withdrawal Assessment Tool (WAT-1) should be completed along with the SBS at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS assessment provides a standard stimulus for observing signs of withdrawal.

**Obtain information from patient record (this can be done before or after the stimulus):**

- Loose/watery stools: Score 1 if any loose or watery stools were documented in the past 12 hours; score 0 if none were noted.
- Vomiting/wretching/gagging: Score 1 if any vomiting or spontaneous wretching or gagging were documented in the past 12 hours; score 0 if none were noted.
- Temperature > 37.8°C: Score 1 if the modal (most frequently occurring) temperature documented was greater than 37.8°C in the past 12 hours; score 0 if this was not the case.

**2 minute pre-stimulus observation:**

- **State:** Score 1 if awake and distress (SBS ≥ 1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative (SBS ≤ 0).
- **Tremor:** Score 1 if moderate to severe tremor observed during the 2 minutes prior to the stimulus; score 0 if no tremor (or only minor, intermittent tremor).
- **Sweating:** Score 1 if any sweating during the 2 minutes prior to the stimulus; score 0 if no sweating noted.
- **Uncoordinated/repetitive movements:** Score 1 if moderate to severe uncoordinated or repetitive movements such as head turning, leg or arm flailing or to and fro movements observed during the 2 minutes prior to the stimulus; score 0 if no (or only mild) uncoordinated or repetitive movements.
- **Yawning or sneezing:** Score 1 if 1 or more than 1 yawning or sneezing observed during the 2 minutes prior to the stimulus; score 0 if no to 1 yawning or sneeze.

**1 minute stimulus observation:**

- **Startle to touch:** Score 1 if moderate to severe startle occurs when touched during the stimulus; score 0 if none (or mild).
- **Muscle tone:** Score 1 if tone increased during the stimulus; score 0 if normal.

**Post-stimulus recovery:**

- **Time to gain calm state (SBS ≤ 0):** Score 2 if it takes greater than 5 minutes following stimulus; score 1 if achieved within 2 to 6 minutes; score 0 if achieved in less than 2 minutes.

**Sum the 11 numbers in the table for the total WAT-1 score (0-12).**

SBS, State Behavioral Scale.


156


