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# Infant populations exposed to prolonged sedation: are they at risk for long-term sequelae?

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# INFANT POPULATIONS EXPOSED TO PROLONGED SEDATION: ARE THEY AT RISK FOR LONG-TERM SEQUELAE?

by

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**INFANT POPULATIONS EXPOSED TO PROLONGED SEDATION:**

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## ABSTRACT

Objective: Opioids are considered standard of care for pain treatment for infants undergoing painful procedures. In addition, prolonged opioid administration is used for sedation during non-surgical treatment (e.g. infants that require intubation and prolonged ventilation). Intubated infants often receive sedative drugs for a prolonged period of time, which leads to opioid dependence and tolerance. The long-term sequelae of such treatment involving the prolonged administration of opioids are unknown. There is evidence in cell cultures and animal models that prolonged opioid exposure is associated with increased neuronal apoptosis (neuronal cell death). In addition, human studies in premature children have suggested that prolonged opioid treatment is associated with decreased visual intelligence, social skills, and memory function. The goal of this study was to identify the population of the youngest patients (less than one year old) that requires prolonged administration of opioids for pain and sedation management. Our overarching hypothesis is that a select group of patients might be at risk for long-term neurologic sequelae from prolonged opioid treatment.

Methods: A retrospective chart review for admission cases over a period of one year was conducted to identify infants that received prolonged administration of opioids and/or benzodiazepines for their treatment. Infants were included if they were less than one year old, full-term (born 37-42 weeks of gestational age), and received prolonged treatment with opioids (e.g. fentanyl, morphine, hydromorphone) and/or benzodiazepines (e.g. midazolam, diazepam, lorazepam). Data on their diagnoses and sedation management at Boston Children's Hospital, including total dose of drugs received and if they developed dependence, was collected.

Results: Out of the 221 charts reviewed, only 46 infants were exposed to prolonged sedation and were full-term. Of these 46 infants, the largest proportion (35%; 16/46) was diagnosed with congenital anomalies. The other diagnoses included respiratory diseases (24%; 11/46), neurological diseases (13%; 6/46), and the remaining infants had a combination of two to three of these diagnoses (28%; 13/46). Infants with congenital diseases had a longer duration of sedation management (59.3 days ± 31.3 days) than infants with respiratory distress/infection (5.9 days ± 3.4 days). Those receiving the longest opioid treatments also exhibited signs of withdrawal when drugs were discontinued, which suggested the development of opioid dependence and required weaning treatment. Patients with sedation for 4 days or less did not show withdrawal

symptoms, while those with sedation of 6 days or more required an opioid and benzodiazepine weaning regimen.

Conclusion: The chart review was valuable from several perspectives. Sedation management at Boston Children's Hospital included prolonged administration not only of opioids, but also benzodiazepines. Such treatment is considered the standard of care. Even otherwise healthy, full-term children that received such sedation for the management of an acute illness (e.g. pneumonia) were at risk for opioid and benzodiazepine dependence if they required intubation and sedation for longer than 4 days. However, the majority of full-term children at risk for potential long-term sequelae of prolonged sedation presented with other confounding factors (e.g. congenital diseases, surgeries, exposure to anesthetic agents). In summary, future research on potential long-term sequelae of prolonged opioid administration should include infants with complex medical diseases as they were exposed to such treatment the longest.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| BIPAP | Bilateral Positive Airway Pressure |
| CDH | Congenital Diaphragmatic Hernia |
| CPAP | Continuous Positive Airway Pressure |
| CT | Computed Tomography |
| ECG | Electrocardiogram |
| EEG | Electroencephalogram |
| fMRI | Functional Magnetic Resonance Imaging |
| ICU | Intensive Care Unit |
| MICU | Medical Intensive Care Unit |
| MRI | Magnetic Resonance Imaging |
| MSICU | Medical Surgical Intensive Care Unit |
| NICU | Neonatal Intensive Care Unit |
| PD7 | Post-Natal Day 7 |
| PAG | Periaqueductal Gray |
| PICU | Pediatric Intensive Care Unit |

## INTRODUCTION

It was not until the 1990s that administration of prolonged opioids and benzodiazepines was considered standard of care for sedation of ventilated infants (Hall, 2009). Prior to this, pain medicine was not administered to the youngest patients under the assumption that infants did not feel pain (Hall, 2009). However, a study by Anand, Hansen, & Hickey (1990) suggested that infants do feel pain and actually have higher stress responses than adults while experiencing pain (e.g. while undergoing surgery). In order to quantify the infants' stress responses, Anand et al. (1990) measured several hormonal and metabolic stress markers, including cortisol and epinephrine, during the perioperative period for surgery. **Figure 1** illustrates the increase in stress indicators during and after surgery (Anand et al. 1990). Surgery was associated with a significant increase in stress markers (plasma epinephrine, norepinephrine, insulin, and glucagon) indicating that infants do feel pain. In addition, the infants that died during the study had higher levels of stress indicators than those that survived. Given this association, decreasing stress indicators may improve survival rates (Anand et al.,1990).

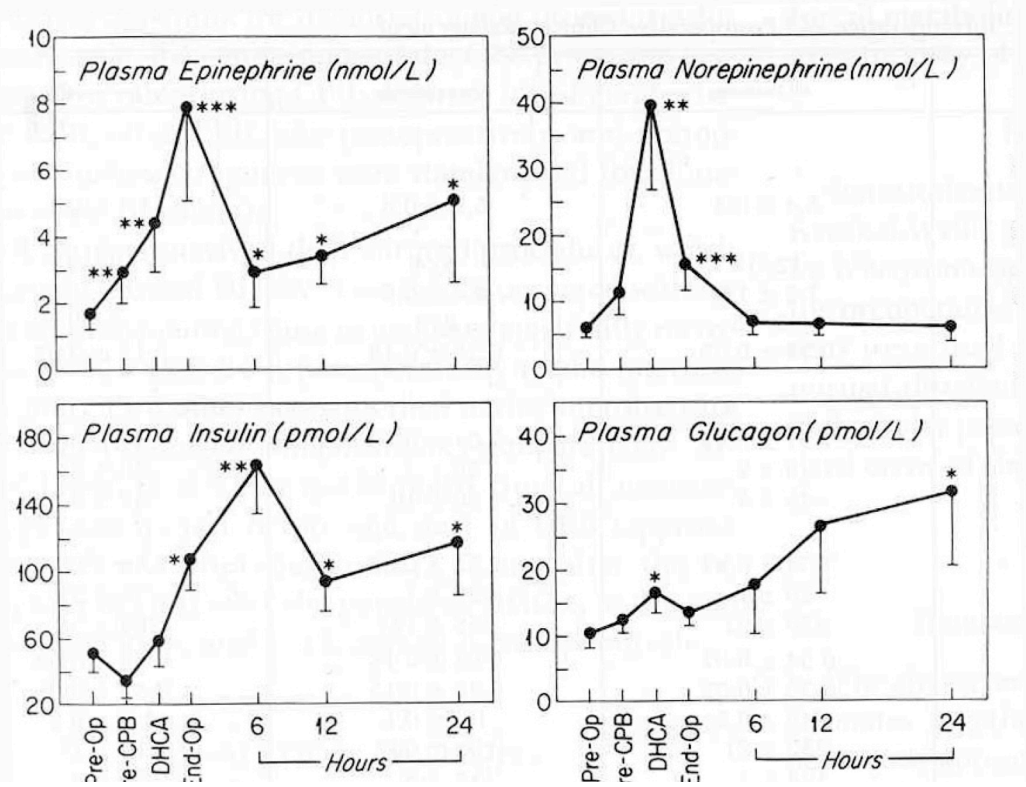


**Figure 1: Perioperative Stress Response in Neonates.** Stress biomarkers for 15 infants with congenital heart diseases were measured during the perioperative period. Data on plasma epinephrine, plasma norepinephrine, plasma insulin, and plasma glucagon were collected. Figure taken from Anand et al., 1990.

In addition to the evidence that untreated pain is associated with perioperative stress, untreated pain is also associated with increases in "heart rate, respiratory rate, intracranial pressure, blood pressure" (Bellù, Waal, & Zanini, 2010) and potential decreases in oxygen saturation that may contribute to the "development of complications such as intraventricular haemorrhage" (Bellù et al., 2010). Pain can also diminish the effectiveness of intubation by disrupting ventilation and breathing patterns (Bellù et al., 2010). We now know that chronic untreated pain in infants interferes with an infant's developing nervous system (Walker, 2013) and is associated with long-term neurologic sequelae. As a result, opioids (e.g.

morphine, fentanyl, hydromorphone) and benzodiazepines (e.g. midazolam, diazepam, lorazepam) have become the standard of care for infants undergoing painful procedures and prolonged sedation (Anand et al., 2010). The World Health Organization currently recommends the use of opioids for infants with moderate to severe pain (WHO, 2012).

**Pain Pathways in Newborns and Infants**

Research over the last 20 years has elucidated differences in pain processing between the developing and adult brain. Since the infant nervous system is still developing and undergoing significant changes, there are important differences between pain pathways in young children and adults (Fitzgerald 2005; Baccei & Fitzgerald, 2005). Based on studies in rat models, developing nervous systems are unique because of intersection between the A-fiber terminals and the C-fiber terminals in the dorsal horn (**Figure 2-2**) (Beggs, Torsney, Drew, & Fitzgerald, 2002; Granmo, Petersson, & Schouenborg, 2008; Fitzgerald & Walker, 2009). Eventually the infant's nervous system matures and these areas become distinct regions; however, while they still intersect, it is difficult for the developing nervous system to differentiate painful inputs from non-painful ones (Fitzgerald & Walker, 2009). Without a well-developed neuronal network, newborns cannot integrate inputs from painful stimuli effectively, resulting in more dispersed pain than in adults (**Figure 2-3**) (Fitzgerald & Walker, 2009). Primary hyperalgesia occurs when the area surrounding an injury causes pain (Woolf, 2007), while secondary

hyperalgesia is characterized by pain occurring outside the initial site of injury (Walker, 2009). While neonates experience primary hyperalgesia like adults (Andrews & Fitzgerald, 2002; Torsney & Fitzgerald, 2002; Ririe, Vernon, Tobin, & Eisenach, 2003), secondary analgesia is not present to the same extent as in mature nervous systems (**Figure 2-4**) (Walker, Meredith-Middleton, Lickiss, Moss, & Fitzgerald, 2007). Furthermore, the neonatal nervous system is characterized by undeveloped descending pain modulatory pathways (**Figure 2-5)**, an immature cortex, (**Figure 2-6)**, and somatosensory responsiveness to painful stimuli (**Figure 2-7**) (Fitzgerald & Walker, 2009).

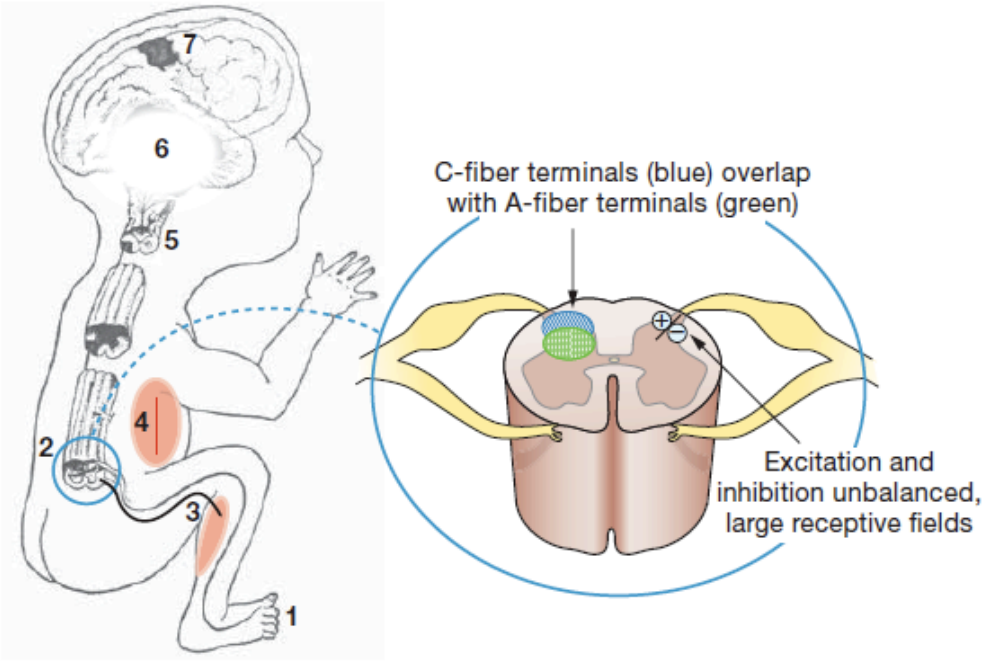


**Figure 2: A Summary of the Neonatal Pain Pathway**. There are several important differences between pain pathways in adults and neonates. In the neonatal dorsal horn, there is overlap between the C-fibers and the A-fibers, leading to more dispersed pain. Figure taken from Fitzgerald & Walker, 2009.

**Importance of Pain Management**

In addition to the short-term effects of anesthesia, there are also long-term benefits of opioid therapy compared to infants not receiving pain management. Several studies have compared premature neonates receiving opioids to control groups not receiving opioid treatment. In a prospective cohort study by Grunau, Oberlander, Witfield, Fitzgerald, & Lee (2001), low birth weight infants underwent a heel stick at 32 weeks after birth to determine their reaction to pain. Compared to infants who did not previously receive morphine, those who had previously received morphine had an improved pain response (Grunau et al., 2001).

In addition to the beneficial effects of pain treatment in acute settings, prolonged administration of opioids has shown to have beneficial effects as well. Specifically, MacGregor, Evans, Sugden, Gaussen, & Levene (1998) analyzed infants who required ventilation and were randomized to morphine or non-morphine solution. At 5-6 years of age, the children were assessed using the Movement Assessment Battery for Children, the Child Behaviour Checklist, and the Weschler Preschool and Primary Scale of Intelligence. While the results were not significant, children who received morphine as infants tended to do better on the scales than those who were ventilated but did not receive morphine (MacGregor et al., 1998). Another study by Anand et al. (1999) reported that children treated with morphine had the least number of neurological complications (e.g. intraventricular hemorrhage and periventricular leukomalacia)

compared with placebo- and midazolam-exposed infants. These neurological outcomes occurred in 32% of the midazolam-treated infants, 24% of the placebo infants, and 4% of the morphine-exposed infants (Anand et al., 1999). Anand et al. (1999) concluded that compared to placebo, morphine infusion may decrease the incidence of neurological outcomes in mechanically ventilated premature neonates. These results suggest that treatment of neonatal pain is essential to normalize pain responses and protect neurological development.

**Opioid Analgesic Mechanism**

Non-opioid analgesics like sucrose can improve behavioral reactions to pain, but these medications do not hyperpolarize neurons to reduce painful sensations (Walker, 2013). In contrast, the administration of opioids is considered effective pain management, as opioids are useful agents to provide effective prolonged sedation in infants (Suresh & Anand, 2001). Opioids bind –μ, –δ, and –κ opioid receptors found in several areas of the nervous system, including the spinal cord, brain, peripheral nociceptors, and the myentric plexus. These receptors also occur on cells such as skeletal and cardiac muscle cells, monocytes, and lymphocytes (Suresh & Anand, 2001). When morphine or other opioids bind these receptors, a signal cascade is activated that leads to hyperpolarization of the neurons (Suresh & Anand, 2001). Specifically, binding of an opioid to an opioid receptor causes the receptor to undergo conformational changes. These changes activate the inhibitory G-proteins $G_0$ and $G_{i\alpha}$, which affect nitric oxide

synthetase and potassium channels and decrease adenylyl cyclase activity, respectively. Through these effects, the neuron becomes hyperpolarized, raising the threshold necessary to depolarize the neuron and propagate an action potential (**Figure 3**). In addition, the amount of neurotransmitter released and the action potential length are reduced. Ultimately, these changes decrease neuronal firing, producing analgesia and sedation (Suresh & Anand, 2001).

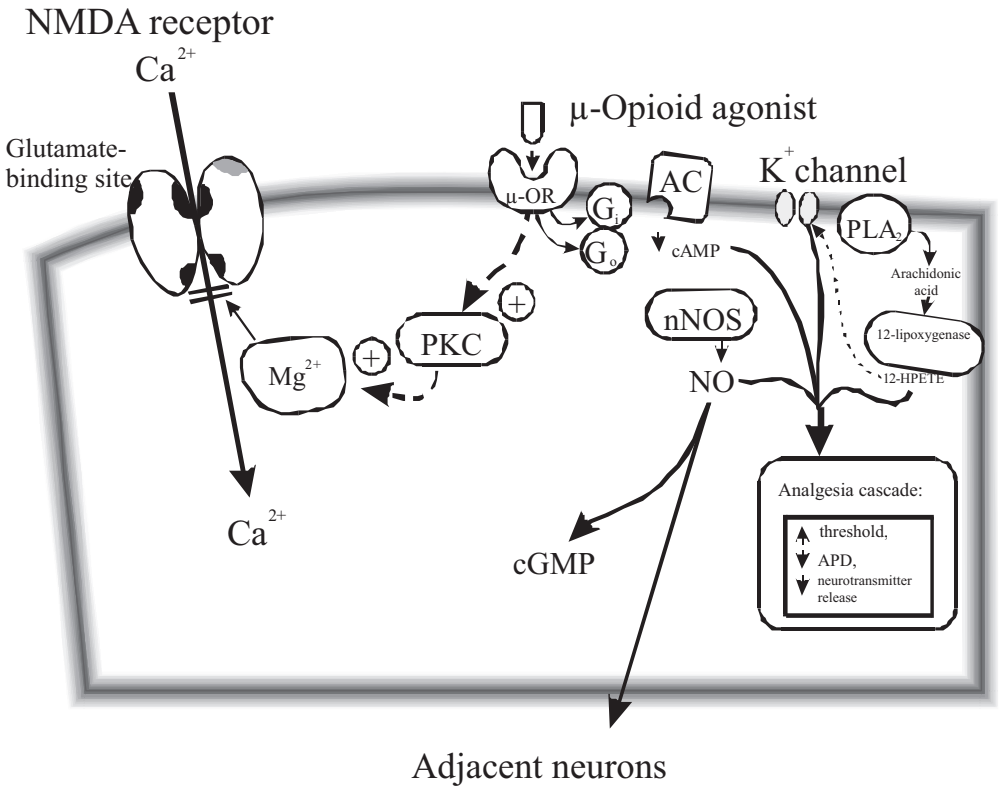


**Figure 3: Mechanism of Opioid Analgesia.** An opioid binds an opioid receptor, which leads to a signal cascade producing analgesia and sedation. Figure taken from Anand et al., 2010.

## Neurological Effects in Animal Models

Apoptosis, or programmed cell death, occurs as a normal part of development for the pruning of neuronal connections. Exposure to opioids, such as morphine and fentanyl, may enhance physiologic apoptosis. Both *in vitro* and *in vivo* models indicate that prolonged opioids are associated with increased apoptosis. Infants are especially susceptible to neurological deficits since their nervous systems are undergoing significant changes. Specifically, normal brain development is characterized by overproduction of neurons and subsequent neuronal pruning (Buss & Openheim, 2004). While this programmed cell death, or apoptosis, is a

necessary part of healthy brain development, external stimuli can also affect this natural process (Blaschke, Staley, & Chun, 2004; Rabinowicz, de Courten-Meyers, Petetot, Xi, & de los Reyes, 1996; Raff et al., 1993; Rakic & Zecevic, 2000). In rat models, stimuli that interfere with natural apoptosis are associated with neurological damage and even death (Kuida et al., 1996). Specifically, Goswami, Dawson, & Dawson (1998) concluded that opioids kill cells through apoptosis by blocking adenylate cyclase in cell culture. An animal study by Emeterio, Tramullas, & Hurlé (2006) found that chronic, but not acute, morphine leads to increased number of apoptotic cells in glial cells and neurons throughout the brain. A study by Mao, Sung, Ji, & Lim (2002) reported increased apoptosis in the adult rat spinal cord after prolonged administration of morphine associated with the development of opioid tolerance. Furthermore, a study by Bajic, Commons, & Soriano (2013) reported that prolonged administration of morphine associated with the development of opioid tolerance leads to increased apoptosis within selected brain regions of developing rat brain: the somatosensory cortex and amygdala (**Figure 4**).

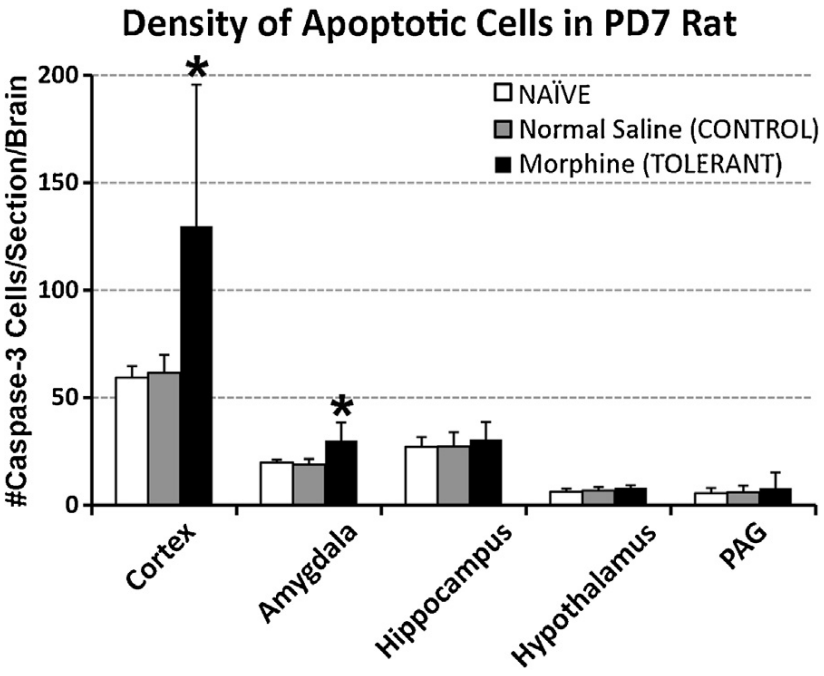


**Figure 4: Density of Apoptotic Cells at Postnatal Day 7 in an Infant Rat Model.** Three groups of infant rats were analyzed at post-natal day seven (PD7): the naïve group did not received any treatment (n=6), the saline group received saline twice daily for 7 days (n=5), and the morphine group received morphine twice daily for 7 days (n=8). The number of apoptotic cells (caspase-3 immunoreactive cells) was analyzed in different brain regions known to be involved in opioid effects. There is a significant increase in the number of apoptotic cells in the cortex and the amygdala, but not the hippocampus, hypothalamus, or periaqueductal gray (PAG). Figure taken from Bajic et al., 2013.

Increased apoptosis in the amygdala and cortex is especially important because these are the areas of the brain involved in opioid processing (Veinante, Yalcin, & Barrot, 2013; Casey et al., 2000). The cortex is involved in somatosensory processing as part of pain pathways (Bushnell et al., 1999), while the amygdala is involved in the emotional-affective dimension of pain, addiction, and possibly in drug-associated memory and drug seeking behavior (Veinante et al., 2013; Koob, 2003; Kruzich & See, 2001). All together, compelling research evidence

suggests that neuronal adaptations might be associated with long-term behavioral and neurologic sequelae.

**Translation of Animal to Human Research**

The evidence on prolonged opioid exposure in animals is concerning for prolonged opioid treatment in human infants. Because there are common features of animal and human neurobiology, there are certain shared factors that can affect whether both animals and humans have long-term sequelae from prolonged opioid exposure. Age, length of exposure, dosage, and pain status may all influence whether a given exposure leads to neurotoxicity (Soriano, 2010). However, within these categories, there are important differences between animals and humans to consider when extrapolating results (see review by Bajic & Soriano, in press). In both rats and humans, there is a critical window of vulnerability during which the nervous system is particularly sensitive to neurotoxic insults (see review by Bajic & Soriano, in press). In rodents, this window extends to postnatal week four (De Felipe, Marco, Fairén, & Jones, 1997; Quinn, 2005; Quincy et al., 2007). For humans, this critical period lasts from the final trimester of pregnancy through 2 years of age (Huttenlocher, 1979). Given this difference in critical periods, it can be difficult to translate neurotoxic exposure in rodent models to humans. Furthermore, analgesic dosage requirements in rat models (5-10 mg/kg) are much higher than in humans (0.1 mg/kg): as much as 100 times greater. Pain also can impact the extrapolation of

animal model results because animals in neurotoxic studies often do not undergo painful procedures. Since untreated pain can have detrimental neurological effects (Anand et al., 1990; Bellù et al., 2010), it is an important factor to consider when evaluating neurotoxic sequelae. Taken together, these limitations highlight the difficulties in extrapolating animal neurotoxicity studies to human infants. Therefore, it is essential to also consider clinical studies on the consequences of prolonged opioid exposure.

**Opioid Tolerance and Withdrawal**

Among neonates undergoing painful procedures, those receiving opioids may have improved outcomes compared to those not receiving opioids, but little is known about the long-term effects of prolonged opioid administration. Infants requiring intubation and mechanical ventilation may receive opioids for a prolonged period of time, which is associated with the subsequent development of opioid tolerance and dependence (Anand et al., 2010). Indeed, withdrawal syndrome (as manifestation of opioid dependence) is very prevalent among infants, with over 35-57% of infants in pediatric intensive care units (PICUs) exhibiting withdrawal symptoms (see review Anand et al., 2010).

Several studies have examined the incidence of tolerance and withdrawal in pediatric patients. Fernández-Carrión et al. conducted a retrospective cohort study of patients in a PICU who received continuous infusions of midazolam or

fentanyl for at least 48 hours. Half of these patients exhibited symptoms of withdrawal, and when only considering patients who received five or more days of infusion, this figure increased to 80%. Of patients exposed to less than five days of infusion, only one patient showed signs of withdrawal. They found that a cumulative fentanyl dose of 0.48 mg/kg, a cumulative midazolam dose of 40 mg/kg, and infusions for at least 5.75 days significantly contributed to whether a child developed tolerance (Fernández-Carrión et al., 2013). Similarly, Bicudo, de Souza, Mângia, & de Carvalho (1999) studied withdrawal in a PICU where children were exposed to fentanyl and midazolam for at least 24 hours (1999). Like Fernández-Carrión et al.'s results, 50% of children showed signs of withdrawal (Bicudo et al., 1999). Furthermore, Franck, Naughton, & Winter (2004) studied 15 children with complex congenital heart disease and/or respiratory failure who received opioids and benzodiazepines for at least four days. Thirteen of these 15 children showed "moderate to severe withdrawal symptoms" (Franck et al., 2004). Children most at risk for withdrawal had cumulative fentanyl dosages of 0.4-1.6 mg/kg, and more withdrawal was seen when fentanyl was added to the morphine treatment (Franck et al., 2004). Similar findings of neonatal abstinence syndrome were reported from a retrospective chart review of infants receiving continuous fentanyl infusions for sedation during extracorporeal membrane oxygenation (Arnold, Truog, Orav, Scavone, & Hershenson, 1990). Over half (57%) of these neonates showed signs of fentanyl tolerance and withdrawal, and fentanyl doses had to increase by

five times to maintain the same analgesic level (Arnold et al., 1990), highlighting the high degree of opioid tolerance. In addition, patients who had a dosage of fentanyl >1.6 mg/kg were much more likely to develop neonatal abstinence syndrome than those with a lower dosage (Arnold et al., 1990). Similarly, Katz, Kelly, & Hsi (1994) conducted a case series to analyze withdrawal in children ages one week to 22 months who required mechanical ventilation and continuous fentanyl infusions. All patients with an infusion duration of nine days or more or a fentanyl dosage of >2.5 mg/kg experienced withdrawal (Katz et al. 1994). Overall, these studies suggest that the duration of sedation and total dosage of opioids and benzodiazepines contribute to the development of tolerance and withdrawal in mechanically ventilated infants.

**Neurological Effects in Human Infants**

In addition to the potential for developing an opioid tolerance, infant opioid exposure may have serious long-term neurological effects (Ferguson, Ward, Paule, Hall, & Anand, 2012; de Graaf et al., 2011). Several studies have analyzed the long-term consequences of neonatal opioid and/or benzodiazepine exposure, but there is still limited evidence of potential long-term neurologic sequelae. Ferguson et al. (2012) followed children who had received morphine as infants 5-7 years later. Although the children had normal intelligence and motor and behavioral development, they had decreased head circumference, decreased memory function, and atypical social skills (Ferguson et al., 2012).

Another study by de Graaf and colleagues (2011) evaluated children at 5 years of age who were ventilated as infants and randomized to morphine or placebo. The children were assessed in several areas, including behavior and intelligence, and morphine was associated with certain long-term neurological consequences. Compared to children who received a placebo, children receiving morphine had significantly impaired executive functioning on one subset of the intelligence test, “visual analysis” (de Graaf et al., 2011).

## SPECIFIC AIMS/OBJECTIVES

Previous research has established that the prolonged administration of opioids is associated with increased apoptosis in animal models. In addition, such treatment is associated with physical and social deficits. There is consensus that opioids are necessary for neonatal pain management, but their long-term consequences are still unknown. Therefore, this study seeks to identify the population of infants that are at highest risk of potential maladaptations at the central nervous systems as a result of prolonged sedation with opioids. Identifying such infants would pave the road for future studies to elucidate the potential long-term sequelae of prolonged opioid treatment. By identifying the group of infants that are exposed to prolonged administration of opioids, this research will contribute to the long-term safety of neonates receiving chronic opioids for sedation and pain management.

We hypothesize that:

1) Healthy infants will be at risk of developing opioid dependence

2) The majority of patients will have other confounding factors (e.g. complex disease, surgeries, exposure to anesthesia)

## METHODS

### Study Design

The study is a retrospective chart review of full-term patients who received prolonged sedation with opioids and benzodiazepines at less than one year of age. A retrospective analysis of patient charts from Boston Children's Hospital was conducted over a period of one year (January 2014-January 2015). Potential subjects were identified through weekly screening of in-house patients as well as screening of infants with a diagnosis of pneumonia or respiratory distress. Inclusion criteria were: full-term (37-42 weeks), less than one year of age, and sedation for at least three days. Prolonged sedation was defined as three or more days of treatment, as similar durations have been associated with withdrawal symptoms in children (Fernández-Carrión et al., 2013; Franck et al., 2004; Bicudo et al., 1999). Information on duration of sedation, length of hospital stay, and Boston Children's Hospital service were collected from patient charts. In addition, total doses of opioids and benzodiazepines were calculated from patient records, and information on diagnostic procedures and respiratory clinical management were collected from patient charts.

## RESULTS

### Chart Review Results

From January 2014-January 2015, a total of 221 patients were screened from several divisions of Boston Children's Hospital: (1) Neonatal Intensive Care Unit (NICU), (2) Medical Surgical Intensive Care Unit (MSICU), (3) Medical Intensive Care Unit (MICU), and (4) Intermediate Care Program at Boston Children's Hospital. Out of the total 221 charts reviewed, 46 patients fit the criteria of being full-term, less than one year old, and receiving prolonged opioids and benzodiazepines, defined as at least three days of continuous infusion treatment.

**Figure 5** describes the diagnoses of these 46 patients. The largest category of infants receiving prolonged opioids and benzodiazepines was those diagnosed with congenital anomalies (35%; 16/46). Of these patients with congenital anomalies, the largest group was infants with congenital diaphragmatic hernia (17%; 8/46), followed by infants with multiple congenital anomalies or syndromes (11%; 5/46). Infants with cardiac congenital anomalies accounted for the remaining 7% (3/46) of the diagnoses. Respiratory diseases composed 24% (11/46) of the diagnoses for these 46 patients. These respiratory diseases consisted of either respiratory distress/infection (17%; 8/46) or other pulmonary diseases (7%; 3/46). Neurological diseases accounted for 13% (6/46) of the diagnoses. Four of these patients with neurological diseases were diagnosed with hypoxic ischemic encephalopathy, one was diagnosed with an anoxic brain

injury, and one was diagnosed with a congenital brain malformation. Since primary neurologic disease can contribute to long-term sequelae, this group was excluded from analysis that involved sedation management. The second-largest group was a combination of two to three of these categories (28%; 13/46).

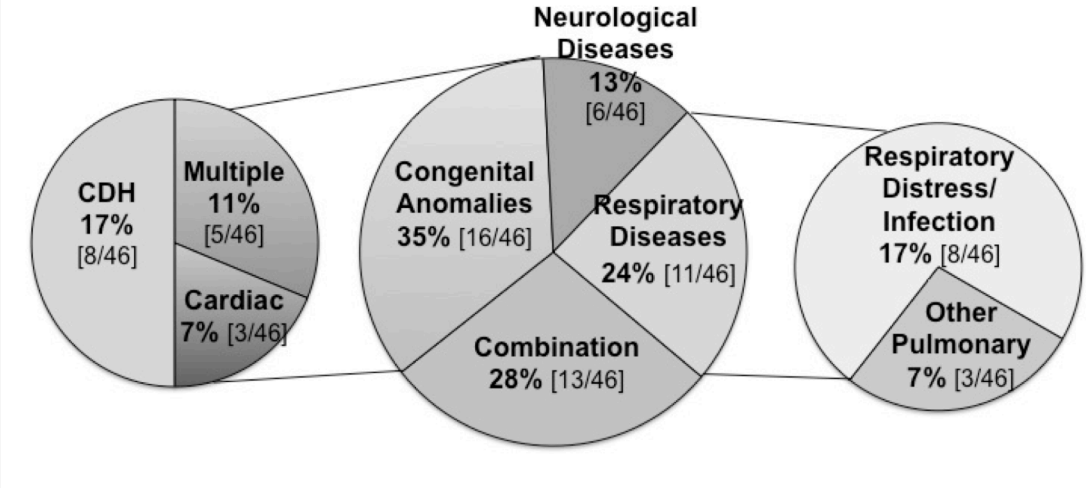


**Figure 5: Diagnoses of Patients Receiving Prolonged Opioids and/or Benzodiazepines.** The figure in the middle illustrates the diagnoses for the 46 infants eligible for analysis. These infants were full-term, less than one year old, and exposed to prolonged sedation. The categories of diagnoses were congenital diseases, respiratory diseases, neurological diseases, and a combination of two to three of these categories. The figure on the left describes the breakdown of congenital anomalies into congenital diaphragmatic hernia (CDH), cardiac, and multiple congenital anomalies. The figure on the right illustrates the breakdown of the respiratory diagnoses into respiratory distress/infection and other pulmonary diseases.

### Patients with Respiratory Distress/Infection

The infants in the respiratory distress/infection group were all full-term (37-42 weeks) and did not have any other significant comorbidities besides the primary diagnosis; they did not have any confounding factors of prematurity, congenital disease, surgeries, or exposure to anesthesia. Five of these patients had

respiratory distress due to respiratory syncytial virus (RSV) infection, two had meconium aspiration syndrome, and one was diagnosed with idiopathic alveolar hemorrhage. All patients presented with some common symptoms that included cough, wheezing, and reduced feeding.

### *Diagnostic Procedures*

Given their respiratory distress, patients received one or more chest x-ray to diagnose and/or follow the progress of the respiratory disease. Patients' x-rays tended to show bilateral lung opacities. Additional radiological tests included abdominal x-rays, abdominal ultrasounds, computed tomography (CT) angiograms, bronchoscopies, and head ultrasounds. Several patients also underwent echocardiograms to rule out cardiac causes of respiratory distress. While some of the echocardiograms showed minor abnormalities, they were consistent with pulmonary hypertension of the newborn. For several patients, additional diagnostic procedures, such as electrocardiograms (ECGs) and electroencephalograms (EEGs), were done to rule out causes other than respiratory distress or infection. None of the procedures required any sedation or anesthesia administration. Results from these procedures were normal.

### *Treatment and Sedation Management*

As defined by the inclusion criteria, all eight patients with respiratory disease/infection were intubated for at least three days while at Boston Children's

Hospital. Three patients were initially given a continuous positive pressure airway pressure (CPAP) trial for respiratory support. Unfortunately, this management escalated to intubation when respiratory distress continued. Six patients were given albuterol nebulizers to help treat their respiratory distress. Since pulmonary infection is a common cause of respiratory distress, all of the infants were started on antibiotics while waiting for blood and urine cultures. The antibiotic course varied between patients, but multiple patients received more than one antibiotic at the time. For sedation management, all eight patients received both opioids (fentanyl or morphine) and benzodiazepines (midazolam) for sedation. **Table 1** summarizes the profile of their sedation management. The average length of inpatient stay at Boston Children's Hospital was 10.1 days ± 4.7 days. There was a range of patient ages; the youngest patient was zero days old, and the oldest was six months old. The average length of sedation was 5.9 days ± 3.4 days. The total amounts of midazolam, morphine, and fentanyl received per patient can be found in **Table 1**. There was a large amount of variability in the total dosages received. The total amount of midazolam received ranged from 13.2 mg-1,429.2 mg. For patients receiving fentanyl, there was a range from 263.6 mcg- 2,212.6 mcg. The four patients treated with morphine received a total dose ranging from 34.4 mg- 108.8 mg.

The treatment location was fairly evenly distributed, with three patients treated in the MICU, three in the NICU, and two patients in the MSICU. The NICU tended

to use fentanyl as the opioid for sedation and pain management, while the MICU and MSICU primarily used morphine. After respiratory stabilization, patients were extubated to either bilateral positive airway pressure (BIPAP) or CPAP, and eventually to a nasal cannula or room air. Three patients also received decadron to minimize airway edema that can be associated with prolonged intubation. Two of the patients had bilateral pneumothoraces, which successfully resolved following chest tube placement under local anesthesia at the bedside.

### *Clinical Outcomes*

Once stable on room air, patients were either discharged home or transferred to a local hospital. Four of the eligible infants required a weaning regimen as they exhibited signs of withdrawal (**Table 1** gray areas). These were the same four infants that were intubated 6 days or longer; the three infants with the shortest periods of intubation (4 days or less) did not require a weaning protocol. The weaning protocols were completed either at Boston Children's Hospital or the patient's local hospital; none of the infants were discharged home on a weaning protocol.

## Patients with Other Pulmonary Diseases

Of the patients with other pulmonary diseases, two patients were diagnosed with persistent pulmonary hypertension and one with pulmonary hypoplasia. All three

patients were admitted on the day of their birth, and they all presented with cyanosis and desaturations at birth.

### *Diagnostic Procedures*

The three infants all had chest x-rays and echocardiograms, and two of the infants underwent ECGs. Two of the patients also had head ultrasounds. All three children had chest tubes placed at the bedside for bilateral pneumothoraces. One infant also underwent a brain magnetic resonance imaging (MRI) and an EEG.

### *Treatment and Sedation Management*

**Table 1** also summarizes the sedation management for the other pulmonary diseases group. The infants diagnosed with other pulmonary diseases had hospital stays ranging from 21 days to 86 days. All infants were initially treated with 100% oxygen or CPAP, but when their respiratory distress persisted, they were intubated and sedated. All patients were exposed to prolonged sedation, with the lengths of intubation ranging from 8.5 days to 42 days. Like the infants with respiratory distress/infection, all patients received opioids (morphine or fentanyl) and benzodiazepine (midazolam) infusions. **Table 1** presents the total doses of fentanyl, morphine, and midazolam per patient. Two of the patients received dopamine and/or epinephrine to maintain mean arterial pressure, and

all three infants received multiple antibiotics at the same time until infection was ruled out.

### *Clinical Outcomes*

All three patients required weaning protocols. Two of the infants were discharged once stable on room air. However, these two infants were both extubated to CPAP before transitioning to room air. One infant was transferred to a local hospital on mechanical ventilation as well as a weaning protocol.

**Table 1: Patients with Respiratory Diseases that Received Prolonged Opioid and Benzodiazepine Sedation**. A summary of the sedation management of the 11 patients with respiratory diseases that required intubation and mechanical ventilation. These infants were full-term, less than one year old, did not have significant comorbidities and were considered otherwise healthy except for the primary lung disease for which they were admitted and received treatment. Patients are arranged based on length of sedation, and age indicates age at admission. The first three patients with respiratory distress/infection did not require a weaning treatment, and the remaining eight patients (as indicated in gray) received six days or longer of sedation that was associated with development of opioid and benzodiazepine dependence and required a weaning treatment. An asterisk in the "Hospital Stay" column indicates that the patient was transferred to another hospital for further management upon discharge from Boston Children's Hospital.

| **Respiratory Distress/Infection** | | | | | | | |
|---|---|---|---|---|---|---|---|
| # | Age | Drugs | Total Dose | **Length of Sedation** | Weaning | Location | Hospital Stay |
| 1 | 0 days | **Fentanyl**<br>Midazolam | 263.6 mcg<br>13.2 mg | **2 days** | N | NICU | 5 days* |
| 2 | 6 months | **Morphine**<br>Midazolam | 38.4 mg<br>39.2 mg | **3 days** | N | MSICU | 4 days |
| 3 | 3 months | **Morphine**<br>Midazolam | 34.4 mg<br>34.4 mg | **4 days** | N | MSICU | 10 days |
| 4 | 1 month | **Fentanyl**<br>Midazolam | 658.8 mcg<br>81.4 mg | **6 days** | Y | NICU | 17 days |
| 5 | 8 weeks | **Morphine**<br>Midazolam | 107.0 mg<br>108.9 mg | **6 days** | Y | MICU | 10 days |
| 6 | 5 months | **Morphine**<br>Midazolam | 108.8 mg<br>1,429.2 mg | **6 days** | Y | MICU | 13 days |
| 7 | 5 weeks | **Morphine**<br>Midazolam | 92.7 mg<br>64.6 mg | **7 days** | Y | MICU | 7 days* |
| 8 | 0 days | **Fentanyl**<br>Midazolam | 2,212.6 mcg<br>97.4 mg | **13 days** | Y | NICU | 15 days* |
| **Other Pulmonary Diseases** | | | | | | | |
| 1 | 0 days | **Fentanyl**<br>**Morphine**<br>Midazolam | 296.3 mcg<br>39.2 mg<br>41.7 mg | **8.5 days** | Y | MSICU | 21 days |
| 2 | 0 days | **Fentanyl**<br>Midazolam | 11,422.5 mcg<br>85.0 mg | **10 days** | Y | NICU | 10 days* |
| 3 | 0 days | **Fentanyl**<br>**Morphine**<br>Midazolam | 5,078.3 mcg<br>268.4 mg<br>676.7 mg | **42 days** | Y | MSICU | 86 days |

**Patients with Congenital Diseases**

As illustrated in **Figure 5**, patient with congenital anomalies comprised total of 35% (16/46) of all the screened patients. **Figure 5** also shows the breakdown of diagnoses for infants with congenital diseases who were full-term, less than one year old, and received prolonged sedation for management of their primary congenital disease. The largest proportion of the children was diagnosed with congenital diaphragmatic hernia (17%; 8/46). The second largest category was infants who had multiple congenital diseases (11%, 5/46), including those with congenital syndromes such as CHARGE syndrome and VACTERL syndrome. Three of the children with syndromes had esophageal atresia as part of their syndrome. The remaining 7% were patients with congenital heart diseases (3/46). Because these infants have complex medical problems, all of the patients in this group underwent at least one surgery at Boston Children's Hospital. Almost half of infants in this group received multiple antibiotics to treat an infection or until infection was ruled out.

***Diagnostic Procedures***

Many of the infants in the congenital diseases group underwent similar diagnostic procedures, including chest x-rays, echocardiograms, and ECGs. Given these patients' complex medical histories, they usually had multiple tests, with some patients having serial procedures. Patients who had seizure activity received

EEGs, and infants on extracorporeal membrane oxygenation were required to undergo a brain MRI. Head ultrasounds and abdominal x-rays were also used in multiple patients.

### *Treatment and Sedation Management*

**Table 2** describes the sedation management for infants diagnosed with congenital diseases and exposed to prolonged opioids and/or benzodiazepines. Because of the severity of the congenital diseases analyzed, these infants often must be intubated and sedated for multiple weeks or months. Infants with congenital anomalies had a much longer length of sedation compared to those with respiratory diseases. **Table 2** presents the lengths of sedation for infants with congenital diseases. Compared to infants with respiratory distress/infection (5.9 days ± 3.4 days), infants with congenital diaphragmatic hernia had an average of 59.3 days ± 31.3 days of sedation, and those with multiple anomalies had an average of 29.3 days ± 26.1 days of sedation. For infants with congenital diaphragmatic hernia, the average length of hospital stay was 111.4 days ± 74.9 days. Patients with multiple congenital diseases had an average length of hospital stay of 104.0 days ± 45.8 days. As several patients were still in the hospital, further follow-up is needed. Like the infants in the respiratory distress/infection subject group, several different services at Boston Children's Hospital were represented in the congenital diseases group.

There were only three full-term patients screened with cardiac congenital anomalies. Their average length of hospital stay was 82.7 days ± 54.1 days. Their length of sedation ranged from 4+ 2 days to 11 days. The patient with 4 + 2 days of sedation received four days of sedation, was extubated, and then reintubated for two additional days of sedation. However, two of these cardiac patients were first admitted to Boston Children's Hospital at several months of age, and there is incomplete sedation information about initial outside treatments.

**Table 2: Infants with Congenital Anomalies Receiving Prolonged Sedation.** Patients with congenital diseases who received prolonged sedation are arranged based on length of sedation. # in the column Hospital Stay indicates patient is deceased, and + indicates the patient was still inpatient at the time of screening. With the exception of the first patient in the cardiac section, all surviving patients required weaning treatment.

| **Congenital Diaphragmatic Hernia** | | | |
|---|---|---|---|
| # | Length of Sedation | Hospital Stay | Location |
| 1 | **19.5 days** | 20 days$^{+}$ | MICU |
| 2 | **39.5 days** | 94 days$^{+}$ | MSICU |
| 3 | **44 days** | 44 days$^{\#}$ | MSICU |
| 4 | **52.5 days** | 170 days$^{+}$ | NICU |
| 5 | **60 days** | 152 days | MSICU |
| 6 | **64 days** | 91 days | MSICU |
| 7 | **68.5 days** | 71 days$^{\#}$ | MSICU |
| 8 | **126.5 days** | 249 days | MSICU |
| **Cardiac** | | | |
| **1** | **4 + 2 days** | 27 days | Cardiology |
| **2** | **6.5 days** | 86 days$^{\#}$ | Cardiology |
| **3** | **11 days** | 135 days | Cardiology |
| **Syndromes/Multiple** | | | |
| **1** | **7.5 days** | 42 days | NICU |
| **2** | **9 days** | 81 days | MSICU |
| **3** | **19 days** | 137 days$^{+}$ | MSICU |
| **4** | **42 days** | 158 days | NICU |

### *Clinical Outcomes*

Three infants, two with congenital diaphragmatic hernia and one with a cardiac congenital anomaly, were deceased at the time of screening. Infants were discharged home on room air or transferred to local hospitals still on respiratory support. However, many infants in this group also required multiple inpatient visits. Except one patient with a cardiac congenital disease, all surviving children underwent a weaning protocol.

## DISCUSSION

This retrospective chart review describes the use of opioids and benzodiazepines for the pain management and sedation of intubated neonates. These cases highlight the significant amounts of opioids and benzodiazepines that infants received while intubated for prolonged periods of time. As infants' brains are still developing, they are particularly susceptible to potential neurological effects of opioids (Anand et al., 2010). It is also essential to understand the management of care of these infants and have insight into which patient groups have treatment associated with potential long-term sequelae.

### Study Limitations

As a retrospective chart review, this study has limitations. Without a comparison group, the chart review is a descriptive study. A chart review also relies on the accuracy and completeness of patient records.

### Sedation Management

Out of the total of 221 charts reviewed, only 46 fit the criteria of being less than one year old, full-term, and receiving prolonged sedation. Of these 46 patients, only eight infants presented as otherwise healthy children less than one year old with respiratory disease requiring intubation, as they had no other significant comorbidities and did not require any surgeries. The infants analyzed had some similar aspects of treatment, such as similar diagnostic procedures and antibiotic

courses, but the chart review highlighted the lack of uniformity in sedation treatment. While all infants received continuous opioid infusions in addition to midazolam infusions, the opioid received varied, tending to depend on the service at Boston Children's Hospital. In accordance with the Boston Children's Hospital Patient Care Manual (2009), sedation management with opioids and benzodiazepines has been done according to the recommended care approach (**Figure 6**).

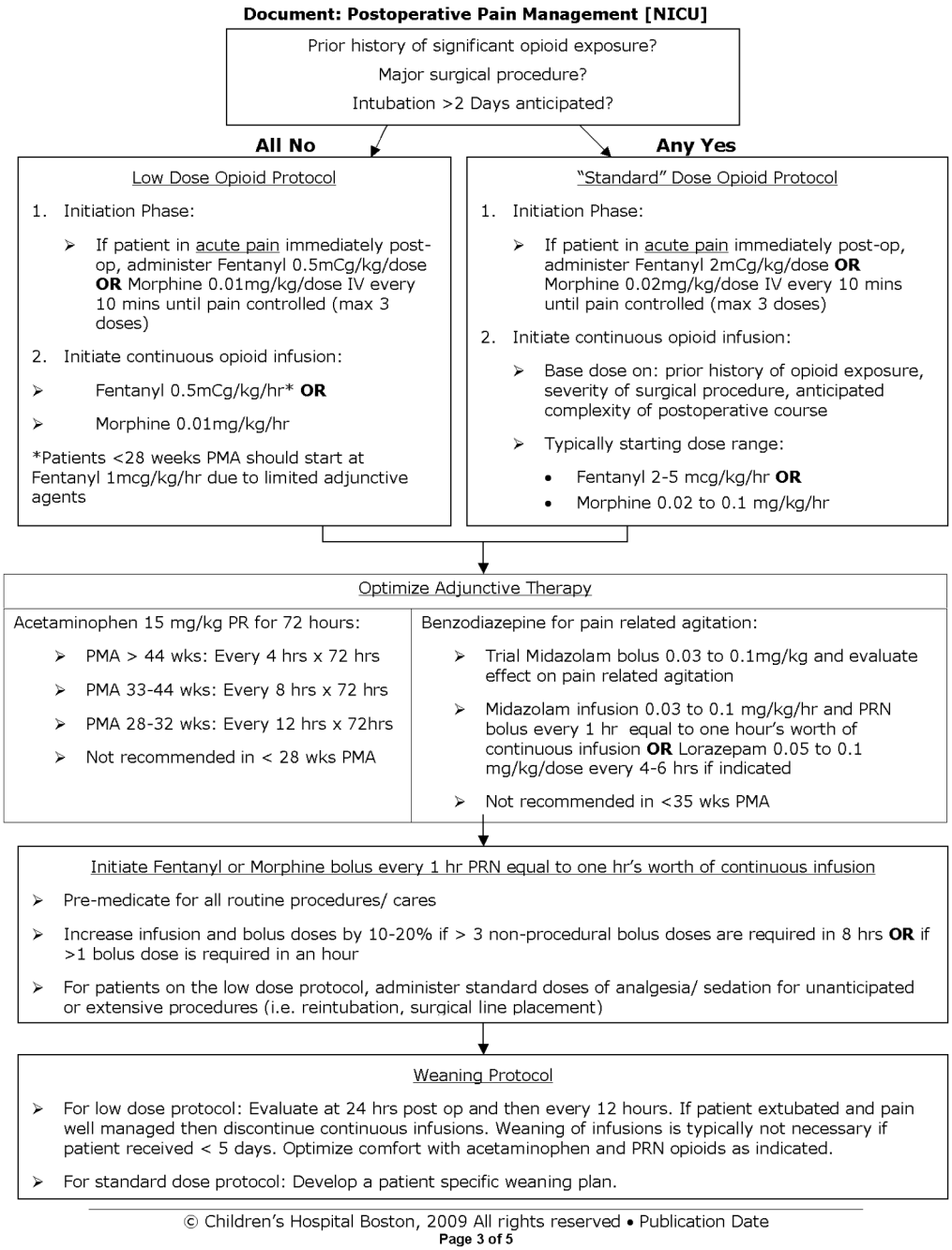





**Figure 6: Boston Children's Hospital Postoperative Pain Management Document.** The Boston Children's Hospital Patient Care Manual outlines recommendations for postoperative pain management. Continuous infusions of opioids and benzodiazepines are recommended for prolonged sedation.

The pattern of withdrawal in these eight patients aligns with previous literature on opioid withdrawal. Similar to previous studies (Fernández-Carrión et al., 2013; Franck et al., 2004, Bicudo et al., 1999; Arnold et al., 1990), our results suggest that infants with short-term opioid therapy do not show signs of withdrawal, while patients with 6 days of treatment or more did show signs of withdrawal. However, the studies by Fernández-Carrión et al., Franck et al., and Bicudo et al. included children older than one year old and did not exclude premature infants. Furthermore, Arnold et al.'s study excluded infants with congenital diaphragmatic hernia. In contrast, we only analyzed full-term infants, and our analysis included infants with congenital anomalies. Overall, short-term sedation is not associated with opioid and benzodiazepine tolerance and withdrawal, suggesting it is a valid therapy for mechanically ventilated infants. However, since prolonged sedation leads to tolerance and withdrawal, more research is necessary to describe potential long-term sequelae.

**Future Studies**

This retrospective chart review suggests that even full-term, otherwise healthy infants are at risk for opioid and benzodiazepine dependence. In addition, infants with congenital diseases have multiple weeks or even months of sedation, putting them at high risk for long-term neurological sequelae. These children had diagnoses of congenital diaphragmatic hernia, multiple congenital anomalies/congenital syndromes, and congenital cardiac diseases. This study

sets the foundation for future analysis by identifying the patient population most at risk for consequences of prolonged opioid exposure.

Specifically, future research is necessary to:

1) Identify structural and functional changes in the human neonatal brain in response to chronic opioid exposure

2) Follow-up patients to identify structural and functional changes in developing brains in response to chronic opioid exposure

Structural MRI and functional magnetic resonance imaging (fMRI) can be used to analyze potential structural and functional neurological changes in the developing infant brain. The use of cognitive and behavioral tests can also help to determine the effects of opioids on neurocognitive function. Since previous research indicates prolonged opioid exposure may be associated with deficits in intelligence subsets (de Graaf et al., 2011), measures of intelligence and school performance may also provide insight into long-term neurological consequences. By improving understanding of this topic, this research will contribute to the safety of neonates receiving chronic opioids.

**Conclusion**

This retrospective chart review shows that full-term infants less than one year old who received opioid or benzodiazepine treatment for 4 days or less did not

require weaning, while those who had treatment longer than 6 days required a weaning protocol. The absence of tolerance and withdrawal with short therapy supports short-term opioid and benzodiazepine sedation as an effective treatment for intubated infants. The lack of tolerance in this short-term treatment suggests that long-term effects may be less likely in this population than for infants receiving longer therapy. However, infants exposed to prolonged sedation are at high risk for long-term sequelae, and thus, more research is necessary to understand the long-term effects of neonatal opioid exposure.

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**CURRICULUM VITAE**

**COLLEEN ANDREWS**
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## EDUCATION

**Boston University School of Medicine**, Boston, MA 2015
Master of Science in Medical Sciences

**Columbia University, Mailman School of Public Health**, New York, NY 2013
Master of Public Health, Epidemiology, Global Health

**Boston College**, Chestnut Hill, MA 2011
College of Arts and Sciences, Arts & Sciences Honors Program
Bachelor of Science in Biology, Hispanic Studies Minor
Dean's List, 2008-2011

**Complutense University of Madrid,** Madrid, Spain Spring 2010
Study abroad, Spanish literature and history

## PROFESSIONAL EXPERIENCE

**Beth Israel Deaconess Medical Center**, Boston, MA Summer 2014
*Emergency Department Assistant*

- Observe patients and communicate behavior changes to staff
- Transport patients between departments
- Maintain a clean and orderly Emergency Department

**Boston Children's Hospital**, Boston, MA Summer 2014
*Department of Anesthesiology, Perioperative and Pain Medicine Intern*

- Recruit participants for clinical research study
- Collect and analyze clinical research data
- Organize operating room materials for Anesthesiologist as an Anesthesia Technician

**Newton-Wellesley Hospital**, Newton, MA Winter 2014
*Emergency Department Volunteer*

- Greet patients and direct them to registration
- Act as a point of contact for waiting patients and families
- Accompany families into the Emergency Department to visit patients

**Helen Keller International**, New York, NY 2013
*Program Assistant*

- Developed a quality assurance toolkit for global nutrition and eye health programs
- Contributed to and reviewed grant proposal drafts
- Organized and annotated technical documents and publications for online staff library

**Helen Keller International**, Patan, Nepal 2012
*Intern*

- Analyzed maternal and child nutrition project data and edited evaluation reports
- Collected evaluation data and conducted interviews during field visits
- Developed case studies on successes and challenges of project components

**Columbia University**, New York, NY Spring 2012
*Teaching Assistant*

- Organized course materials for Environmental Health Sciences course
- Graded homework, papers, quizzes, and exams for 40 students
- Led office hours and review sessions to clarify course content

**Massachusetts General Hospital YouthCare**, Boston, MA Summer 2011
*Assistant Group Leader*

- Taught social thinking skills for a group of children with autism
- Planned and executed lesson plans using visuals and social stories
- Developed individualized social and behavioral goals and monitored progress

**Boston College**, Boston, MA Fall 2010
*Teaching Assistant*

- Organized course materials for 50 students in a Microbiology course
- Ran individual seminars for students to facilitate understanding of course materials
- Directed review sessions for students to clarify course information before exams

**Boston College**, Chestnut Hill, MA Summer 2010
*Undergraduate Research Fellowship*

- Conducted biological research on transposons in yeast DNA in university laboratory
- Analyzed data for presentation to laboratory colleagues on research and results
- Evaluated success of project and restructured procedure as necessary
- Contributed to formulating experimental design

**Massachusetts General Hospital**, Boston, MA 2008-2010
*Pediatric Hematology and Oncology Volunteer*

- Supervised pediatric hematology and oncology patients and their siblings
- Provided emotional support for families and created activities for patients
- Assisted with special events preparations

**La Casa de Esperanza, Inc.**, Milwaukee, WI Summer 2009
*HIV/AIDS Prevention and Education Program volunteer*

- Presented HIV/AIDS educational information in Spanish to Hispanic families
- Collaborated to design a HIV/AIDS public health program targeting Hispanic men
- Researched and organized facts and prevention strategies for use in presentations
- Planned weekly support groups for Hispanic men with HIV/AIDS

## AWARDS

Sasakawa Young Leaders Fellowship Fund Summer Grant 2012

- Awarded through the Weatherhead East Asian Institute at Columbia University to students who demonstrate academic excellence and a commitment to Southeast or East Asia
- Grants partial funding for students to conduct research or internships in Southeast Asia