Infant populations at risk for possible short-term and long-term consequences after exposure to prolonged sedation

Liu, Tiffanie
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by

TIFFANIE LIU
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INFANT POPULATIONS AT RISK FOR POSSIBLE SHORT TERM AND LONG-TERM CONSEQUENCES AFTER EXPOSURE TO PROLONGED SEDATION

TIFFANIE LIU

ABSTRACT

Introduction: Prolonged sedation treatment in neonatal pediatric populations is associated with opioid and benzodiazepine tolerance, dependence, and withdrawal syndrome. Despite the clinical relevance of this problem, we have limited knowledge of the long-term repercussions. Current literature focuses on premature neonates and suggests that opioid exposure may cause neurodevelopmental sequelae. The main objective of this literature review was to investigate what infant populations are at risk of developing short-term and/or long-term consequences from prolonged infantile sedation exposure.

Published Studies: A literature review was conducted on previous studies that focused primarily on the effects of opioids and benzodiazepines on infants and how it may affect the future development in these children. Studies show that short-term consequences include increased heart rate, increased respiratory rate, increased blood pressure, intracranial pressure fluctuations, and risk of further complications such as intraventriculat hemorrhage (IVH), periventricular
leukomalacia (PVL), or even death. Long-term repercussions include the possibility of decreased brain volume, decreased head circumference and body weight, intelligence deficits, and social and behavioral issues.

**Discussion:** Standard pain and sedation management involves the use of opioids and benzodiazepines. Treatment duration and medication dosage depend on severity of the patient’s illness. Since prolonged sedation administration is often associated with tolerance and dependence, future research (such as long-term follow up of these infants at later neurological milestones) is necessary to determine possible short-term and long-term neurological and behavioural sequelae for infants exposed to prolonged treatment with opioids and benzodiazepines. Standardized pain and sedation management guidelines may also increase the effectiveness of treatment and drug administration.
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LIST OF ABBREVIATIONS

ICU ......................................................... Intensive Care Unit
IVH ......................................................... Intraventricular Hemorrhage
MRI ......................................................... Magnetic Resonance Imaging
NEOPAIN .................. Neurologic Outcomes and Preemptive Analgesia in Neonates
NICU ....................................................... Neonatal Intensive Care Unit
NOPAIN ..................... Neonatal Outcomes and Prolonged Analgesia in Neonates
PAD ......................................................... Pain, Agitation, and Delirium
PICU ....................................................... Pediatric Intensive Care Unit
PVL ......................................................... Periventricular Leukomalacia
SBS ........................................................ State Behavior Scale
WAT-1 .................................................... Withdrawal Assessment Tool-1
INTRODUCTION

Prolonged use of opioids and benzodiazepines is common practice for the pain and sedation management of the youngest of patients. This type of treatment is now considered our standard of care but prior to the 1990s, medications for pain were not administered to infants under the assumption that they could not feel any pain (Hall, 2007). Little was known about a newborn’s bodily responses to severe stress until Anand, Hansen, and Hickey conducted a study in 1990. Their study suggested that infants not only do feel pain, but they may have more extreme stress responses than adults when experiencing pain. To quantify stress responses, hormonal and metabolic stress markers were measured in the perioperative period of surgery for each individual infant (Anand et al., 1990). Figure 1 displays the measurement of the selected stress indicators during and up to 24 hours after surgery. Since the surgery was associated with a substantial increase in the chosen stress markers (plasma epinephrine, plasma norepinephrine, plasma insulin, and plasma glucagon), it indicated that infants do indeed feel pain (Anand et al., 1990). Furthermore, infants that died during the study had more extreme hormonal stress responses and more extreme metabolic responses (such as hyperglycemia, high lactate concentrations, high blood alanine concentrations, etc.) when compared to the infants that survived. From this information, it can be inferred that decreasing the levels of the stress indicators may improve the rate of survival. (Anand et al., 1990).
FIGURE 1: Hormonal changes (perioperative stress response) in neonates. Stress biomarkers for 15 infants with congenital heart diseases were measured. Data on plasma epinephrine, plasma norepinephrine, plasma insulin, and plasma glucagon were collected during the perioperative period and up to 24 hours afterwards. This data is compared to the preoperative baseline. Figure from Anand et al., 1990.

Not only is there evidence that untreated pain is associated with detrimental perioperative stress (possibly leading to death), but untreated pain may also have direct consequences on the acute illness of the newborn, as well as current and future development of the newborn. (Bellu et al., 2010). Untreated pain may lead to short-term consequences such as fluctuation and instability of the heart rate, respiratory rate, intracranial pressure and oxygen saturation of the blood,
blood pressure, and even lead to further complications (Anand, 1997). Pain may also disrupt ventilation and breathing patterns, therefore lessening the effectiveness of intubation (Bellu et al., 2010).

So now that we know that infants, like older children and adults, do feel pain, more studies have been conducted, widening our scope of knowledge into the previously unknown world of neonatal pain. Infants and young adolescents actually have decreased pain thresholds and increased physiological responses to painful stimuli when compared to adults and older children (Craig, 1993). Chronic untreated pain may affect the developing infant’s brain and nervous system, resulting in long-term consequences (Anand et al, 1990). Sedation medications are thereby used to treat pain, in hopes of increasing comfort and preventing the effects of chronic untreated pain. Recommendations on a more aggressive approach to treating and preventing pain have actually been suggested (Bellu et al., 2010) but there are still uncertainties about the possible risk of long-term consequences from sedation medications (particularly opioids).

Opioids such as fentanyl, hydromorphone, and morphine are administered to relieve pain in infants undergoing surgery or other painful procedures. Opioids are often used in combination with benzodiazepines such as diazepam, lorazepam, and midazolam for sedation of critically ill infants to reduce stress and agitation, especially during intubation and mechanical ventilation (Anand, 2001).
While these efforts have been proven to decrease stress and increase comfort for mechanically ventilated infants, such treatment is associated with high incidence of tolerance and dependence (Anand et al., 2010) and the possibility of acute and long-term sequelae is still widely unknown.

**Consequences of Untreated Pain**

In the last two decades, research and studies have revealed differences in pain processing between an infant’s developing brain and an adult brain. The nervous system of an infant is still developing and undergoing significant change. Research suggests that strong painful procedures or mild repeated procedures performed on infants may permanently modify their pain processing (Hatfield, 2014). This may lead to long-term changes affecting the brain, neurodevelopment, pain modulation, and reactivity later in adulthood. Undermanaged acute pain in early childhood is considered to be the greatest risk factor for the development of chronic pain in children and adults (Hatfield, 2014).

Undermanaged pain in neonates leads to both short-term and long-term consequences. Short-term consequences of painful procedures include decreased oxygen saturation, increased heart rate, fluctuation in intracranial pressure, and increased levels of epinephrine, norepinephrine, insulin, and glucagon (Bellu et al., 2010; Hatfield, 2014). Fluctuations in intracranial pressure and cerebral blood volume increase the risk of complications such as IVH.
(Kaneyasu, 2012). Newborns may experience substantial pain as a result of acute or chronic illness, surgery, intubation, or intensive care treatment. These bouts of pain – treated or not - may result in tissue injury that may alter the development of pain pathways (Li, 2009).

Injury or inflammation to the dorsal horn network in early life may contribute to altered development in spinal nociceptive processing. The neonatal brain and spinal cord are particularly vulnerable to stress and pain exposure since this is a crucial time for development and maturation. Noxious insults, surgical procedures, and repetitive pain or stress related exposures might permanently modify the development of the immature nervous system (Ranger, 2014). It is hypothesized that long-term consequences may be linked to the plasticity of the neonate’s nervous system and altered neurodevelopment. This may mean that in adulthood, pain sensitivity may be altered; for example, increased sensitivity to pain in certain areas may remain and could result in hyperalgesia (Hatfield, 2014). Studies in the preterm infant have shown that repeated pain or stress may cause long term consequences such as altered somatosensory processing (Abdulkader, 2008), pain sensitivity (Grunau, 2001), and response to pain (Grunau, 2005). For example, infants that required treatment in the NICU had an abnormally lowered threshold to tonic heat and mechanical touch when compared to controls (Abdulkader, 2008), which indicates an altered central sensitization (Ranger, 2014). Central sensitization in adulthood may lead to
prolonged states of chronic pain (Schwaller, 2014). These studies had findings of hypersensitivity, but hyposensitivity was also demonstrated in older children who had experienced a previous surgery and stay in the NICU as neonates (Walker, 2009). Not only is the nervous system altered, but brain development may be as well. Increased exposure to painful or stressful procedures for preterm infants in the NICU was associated with reduced brain size, altered brain functional connectivity, and total brain injury (Inder et al., 2011). Alterations in neurobehaviour were also a result of infant stress exposure (Inder et al., 2011).

Because of all the evidence pointing to short-term and long-term consequences of untreated or undermanaged pain, it is important for physicians and caretakers to adequately manage pain, particularly in newborns and infants. Adequately managing neonatal pain may be necessary for normal pain responses and neurological development (Anand et al., 1999). In the Neonatal Outcomes and Prolonged Analgesia in Neonates (NOPAIN) trial performed by Anand and colleagues (1999), benefits of analgesia and sedation for preterm neonates were demonstrated. The study suggested that morphine analgesia or midazolam sedation might improve neurologic outcomes for preterm neonates requiring mechanical ventilation when compared to no pain management. The results of this study are shown in FIGURE 2 (Anand et al., 1999).
FIGURE 2: Neurologic Outcomes. 67 preterm neonates that required ventilator support were separated into 3 groups receiving midazolam hydrochloride, morphine sulfate, or placebo. Poor neurological outcomes occurred in 24% of the placebo group, 4% of the morphine group, and 32% of the midazolam group. Graph taken from Anand et al., 1999.

The study indicates that the infants given morphine had a lower number of poor neurologic outcomes (such as IVH and periventricular leukomalacia, PVL) as opposed to the neonates receiving midazolam or placebo for treatment. These results suggest that preterm neonates on ventilator support who were administered a low-dose morphine infusion had reduced incidences of poor neurological outcomes (Anand et al., 1999). Due to the low sample size of the NOPAIN study, a future study would be necessary to confirm the results.
The NOPAIN pilot study led to a second study performed by Anand and his colleagues. The Neurologic Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial was conducted to investigate the effect that preemptive administration of morphine could have on ventilated preterm infants. The morphine was found to decrease early neurologic injury, although it made no difference in the risk of severe IVH, periventricular leukomalacia, or death (Anand et al., 2004). Therefore, the use of opioids and benzodiazepines may not only prove to be beneficial in protecting the neonate's neurological development, but may also help prevent short-term and long-term consequences of chronic untreated pain.

**Importance of Pain Management**

We now know that chronic untreated pain is detrimental to the developing neonate's nervous system and neurological development. There are major benefits to using sedation to combat repeated stress or pain exposure in pediatric patients undergoing surgical procedures or mechanical ventilation, but are there adverse events (Grant, 2013) that could arise from prolonged sedation? Short-term consequences of prolonged opioid and benzodiazepine administration in infants such as tolerance, dependence, and withdrawal are known (Anand et al., 2010; van Dijk et al., 2007). But possible long-term sequelae from prolonged exposure to opioids and benzodiazepines are consequences that infants may also be at risk for. Children and adults in need of intubation are routinely
administered sedation medications. They have clear guidelines for the dosages of the medications necessary to treat the pain. But there is infinitely more variability in the approach to administering sedation medications to neonates. Since it was previously believed that infants did not feel any pain, this false notion may have accounted for the low usage of anesthetics for infants. According to Anand’s paper in 1997, opioids were being underutilized in neonatal intensive care units (NICUs). Infants are not able to verbally communicate their level of pain to their caretakers, resulting in the underestimation – or overestimation – of the medications necessary for adequate treatment.
PUBLISHED STUDIES

Our knowledge of the long-term effects following postnatal opioid exposure is limited; research in premature neonates suggests that prolonged sedation exposure is associated with possible neurodevelopmental sequelae such as alterations in cerebral structure and possible neurobehavioral problems (Ferguson, 2012; McPherson et al., 2015). This literature review seeks to identify a population of infants with history of prolonged sedation associated with opioid and benzodiazepine dependence that are at risk for short-term consequences, also putting them at high risk for developing potential long-term sequelae.

Current standard of care for infants undergoing painful procedures calls for administration of sedation medications. Opioids such as fentanyl and morphine and benzodiazepines such as lorazepam and midazolam are most often used for pain management. Pain management is supported by clinical evidence (Anand et al., 1999; Anand et al., 2004). However, much is still unknown about the repeated use or prolonged drug administration in the sedation of infants.

**Sedation Medications: Opioids and Benzodiazepines**

Opioids and benzodiazepines are commonly used together for sedation management. Opioids have long been known to produce tolerance and dependence when administered via continuous intravenous infusion. Morphine
and fentanyl are used to manage pain differently. Morphine is a longer lasting drug, used for extended pain and sedation, such as chronic pain from surgical procedures (Silva, 2007). Fentanyl is a faster acting drug, more potent dose-for-dose than morphine. In the case of intubation, fentanyl is often used since the long-acting (and therefore slow acting) morphine may cause a delay in sufficiently relaxing an infant’s airway at the time of laryngoscopy or intubation (Silva, 2007). Since fentanyl is faster acting, it also lasts for a shorter duration than morphine.

Morphine and its effects have been more widely studied than fentanyl. Morphine has been widely used via continuous intravenous infusions for treating postoperative pain. In the cases of necessary intubation or mechanical ventilation, some studies have shown that morphine may no longer be the best choice (Kabara, 2015). Morphine causes respiratory depression, so for infants in requiring ventilator support, use of this drug could be detrimental. Fentanyl is faster acting in pain relief and sedation while also being superior to morphine when it comes to respiratory depression (Kabara, 2015), meaning it can be administered as a continuous infusion for postoperative pain instead of morphine.

Opioids are known to induce tolerance and dependence particularly if used for prolonged durations. Prolonged sedation is defined as more than 72 hours of continuous sedation (Thornton and Smith, 1997) since drug tolerance rarely
occurs before this point. Iatrogenic tolerance occurred when the given dose of a drug (in this case, morphine) was no longer effective and a larger dose became necessary to induce the same effects (analgesic level) as before (Thornton and Smith, 1997). Physical dependence could be seen when the drug use was discontinued and there were signs of withdrawal. Morphine studies in rats have shown that tolerance occurs after repeated or continuous exposure, although studies do not agree on the exact time tolerance occurs (Fanselow and Cramer, 1988; Barr and Wang, 1992). In each of these studies, morphine was administered via bolus injection with different dosages and schedules, possibly accounting for the discrepancy. Another possible reason for their different results may have been due to the stress induced when handling and injecting the rat (Thornton and Smith, 1997). To remove these unwanted variances, Thornton and Smith (1997) used minipumps (as shown in Figure 3) to deliver the drug at a constant rate to the rats in order to test their hypothesis that continuous fentanyl administration could cause tolerance and dependence.
FIGURE 3: Osmotic Minipumps. Handling and manually injecting the neonatal rat with fentanyl causes stress, possibly creating variations in the results. The minipump implanted into infant rat for continuous infusion of fentanyl would reduce the unwanted handling stress and create a more cohesive and organized schedule for treatment of each rat. Photo taken from Thornton and Smith, 1997.

While opioids are mostly used in the event of treating pain, benzodiazepines such as diazepam, lorazepam, and midazolam are used primarily for their sedative effects. Benzodiazepines are used to treat agitation as well as for withdrawal symptoms. For infants, opioids are used in combination with benzodiazepines for sedation management. Reports suggest that benzodiazepines used in high doses or extended durations may cause serious adverse effects (Ng, 2002; Uzun, 2010), although this has yet to be proven.

Pain and Sedation Management

Even the youngest of patients are treated with medications such as opioids and benzodiazepines for the management of pain and sedation. While there are clear guidelines for treating adults in intensive care units (ICU) (Figure 4), there is still great variability in the treatment of infants in the NICU.
### Assess and Treat

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<td><strong>PAIN</strong></td>
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<tr>
<td>• Pain assessment should be routinely performed in all ICU patients (1B).</td>
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<td>• Self report is preferred over the use of behavioral pain scales to assess pain in ICU patients who are able to communicate (B).</td>
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<tr>
<td>• The BPS and CPOT are the most valid and reliable behavioral pain scales for use in ICU patients who cannot communicate (B).</td>
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<td>• Vital signs should not be used alone to assess pain, but they may be used adjunctively for pain assessments (2C).</td>
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<td>• Preemptively treat chest tube removal with either analgesics and/or non-pharmacologic therapy (1C).</td>
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<tr>
<td>• Suggest preemptively treating other types of procedural pain with analgesic and/or non-pharmacologic therapy (2C).</td>
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<tr>
<td>• Use opioids as first line therapy for treatment of non-neuropathic pain (1C).</td>
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<tr>
<td>• Suggest using non-opioid analgesics in conjunction with opioids to reduce opioid requirements and opioid-related side effects (2C).</td>
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<tr>
<td>• Use gabapentin or carbamazepine, in addition to intravenous opioids, for treatment of neuropathic pain (1A).</td>
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<tr>
<td>• Use thoracic epidural for postoperative analgesia in abdominal aortic surgery patients (1B).</td>
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<td>• Suggest thoracic epidural analgesia be used for patients with traumatic rib fractures (2B).</td>
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<td><strong>AGITATION</strong></td>
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<td>• Depth and quality of sedation should be routinely assessed in all ICU patients (1B).</td>
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<td>• The RASS and SAS are the most valid and reliable scales for assessing quality and depth of sedation in ICU patients (B).</td>
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<td>• Suggest using objective measures of brain function to adjunctively monitor sedation in patients receiving neuromuscular blocking agents (2B).</td>
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<td>• Use EEG monitoring either to monitor non-convulsive seizure activity in ICU patients at risk for seizures, or to titrate electroencephalographic medication to achieve burst suppression in ICU patients with elevated intracranial pressure (1A).</td>
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<td>• Target the lightest possible level of sedation and/or use daily sedative interruption (1B).</td>
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<td>• Use sedation protocols and checklists to facilitate ICU sedation management (1B).</td>
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<td>• Suggest using analgesia-first sedation for intubated and mechanically ventilated ICU patients (2B).</td>
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<td>• Suggest using non-benzodiazepines for sedation (either propofol or dexmedetomidine) rather than benzodiazepines (either midazolam or lorazepam) in mechanically ventilated adult ICU patients (2B).</td>
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<tr>
<td><strong>DELIRIUM</strong></td>
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<tr>
<td>• Delirium assessment should be routinely performed in all ICU patients (1B).</td>
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<td>• The CAM-ICU and ICDSC delirium monitoring tools are the most valid and reliable scales to assess delirium in ICU patients (A).</td>
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<td>• Mobilize ICU patients early when feasible to reduce the incidence and duration of delirium, and to improve functional outcomes (1B).</td>
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<td>• Promote sleep in ICU patients by controlling light and noise, clustering patient care activities, and decreasing stimuli at night (1C).</td>
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<td>• Avoid using rivastigmine to reduce the duration of delirium in ICU patients (1B).</td>
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<td>• Suggest avoiding the use of antipsychotics in patients who are at risk for torsades de pointes (2B).</td>
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<tr>
<td>• Suggest not using benzodiazepines in ICU patients with delirium unrelated to ETOH/benzodiazepine withdrawal (2B).</td>
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## Summary of PAD Guidelines

### Pain and Analgesia
1. ICU patients routinely experience pain at rest and with ICU care (B). Pain in cardiac surgery patients, especially women, is poorly treated (B). Procedural pain is common in ICU patients (B).
2. Perform routine pain assessment in all patients (1B). In patients unable to self-report, we suggest using behavioral pain scales other than vital signs to assess pain (2C). The BPS and CPOT are the most valid and reliable behavioral pain scales (B). Vital signs should only be used as a cue for further pain assessment (2C).
3. For non-neuropathic pain, use intravenous opioids as first-line analgesic therapy (1C); use non-opioid analgesics to reduce opioid side effects (1C); and use gabapentin or carbamazepine in conjunction with intravenous opioids for neuropathic pain (1A).
4. Suggest preemptively treating procedural pain (2C), especially chest tube removal (1C).
5. Use thoracic epidural analgesia for abdominal aortic surgery (1B), and suggest also using for traumatic rib fractures (2B). No evidence guides the use of lumbar epidural analgesia for abdominal aneurysm surgery (0A), or thoracic epidural analgesia for either intrathoracic or nonvascular abdominal surgical procedures (0B). No evidence guides the use of regional vs. systemic analgesia in medical ICU patients (0).

### Agitation and Sedation
1. Maintaining lighter levels of sedation in ICU patients is associated with improved clinical outcomes (B); light levels of sedation should be maintained in these patients (1B).
2. The RASS and SAS scales are most valid and reliable instruments for assessing adequacy and depth of sedation (B).
3. Use Brain Function monitors only as adjuncts to subjective sedation scales in unparalyzed patients (1B), but suggest using brain function monitors to primarily monitor depth of sedation in patients receiving neuromuscular blocking agents (2B).
4. Use EEG monitoring to monitor non-convulsive seizure activity in ICU patients at risk for seizures, and to titrate burst suppression therapy in ICU patients with elevated intracranial pressure (1A).
5. Use either use daily sedative interruption or titrate sedative medications to maintain light levels of sedation (1B). Suggest using Analgesia-first sedation (2B). Suggest using non-benzodiazepines rather than benzodiazepine infusions for sedation (2B). Use sedation protocols and daily checklists to integrate and facilitate management of pain, sedation, and delirium in ICU patients (1B).

### Delirium
1. Delirium is associated with increased mortality (A), prolonged ICU and hospital LOS (A), and post-ICU cognitive impairment (B).
2. Delirium risk factors include: pre-existing dementia, HTN, history of alcoholism, and a high severity of illness at baseline (B); coma (B); and benzodiazepine use (B). Mechanically ventilated ICU patients at risk for delirium have a lower delirium prevalence when treated with dexmedetomidine rather than with benzodiazepines (B).
3. Routinely monitor ICU patients for delirium (1B). The CAM-ICU and ICDSC are the most valid and reliable instruments for this purpose (A).
4. Pursue early mobilization to reduce the incidence and duration of delirium (1B).
5. Suggest not using either haloperidol or atypical antipsychotics prophylactically to prevent delirium (2C).
6. Promote sleep in adult ICU patients by optimizing patients’ environments, using strategies to control light and noise, to cluster patient care activities, and to decrease stimuli at night in order to protect patients’ sleep cycles (1C).
7. Do not use rivastigmine to reduce the duration of delirium in ICU patients (1C).
8. Suggest withholding antipsychotics in patients with baseline QT prolongation, a history of Torsades de Pointes, or in those receiving concomitant medications known to prolong the QT interval (2C).
9. When sedation is required in delirious ICU patients, suggest using dexmedetomidine rather than benzodiazepine infusions for sedation in these patients, unless delirium is related to either alcohol or benzodiazepine withdrawal (2B).

**FIGURE 4:** Pain, agitation, and delirium (PAD) recommendations for adults in ICUs. Figure taken from Barr et al., 2013.
The guidelines from Figure 4 give in depth directions for assessing and treating PAD in adults in the ICU. Not only are these guidelines given, but there is also a second set of instructions (Figure 5) for treatment (Barr et al., 2013), providing the physician or caretaker with a template for PAD care. These recommendations take into consideration not only how and what the patient is feeling, but also the ease of the physician to assess the patient and determine the best path of care. The goal of these guidelines is to optimize patient care and management in the ICU (Jacobi et al., 2002; Barr et al., 2013).
FIGURE 5: ICU PAD care bundle. A and B show easy to follow practice guidelines that are most likely to improve the patient’s outcome. Figure taken from Barr et al., 2013.
Self-reporting is a great asset in determining the treatment plan for pain in an adult in the ICU. But infants cannot self-report. This makes it much more difficult to determine how much pain the infant is in, since infants often cry but not always due to pain and agitation. The pain level directly influences the choice of medication and dose of medication necessary to adequately treat the pain. A study conducted by Martha Curley (who is widely known for her research and work related to the clinical management of critically ill infants) in 2006 developed and tested the State Behavioral Scale’s (SBS) reliability in describing agitation and sedation levels in infants requiring ventilator support. The SBS (Figure 6) was designed to help physicians evaluate what sedation level is necessary and appropriate for the infant undergoing a painful procedure (Curley, 2006). While we have mostly overcome the issue of undermanaged pain, the risk of over-sedation still poses a problem. Since patients in the NICU are particularly vulnerable, the SBS has been used to help nurses and physicians to quickly and accurately assess and treat their young patients.
FIGURE 6: State Behavioral Scale (SBS). Behavioral assessment tool and rating scale for agitation. Figure taken from Curley, 2006.

Using a standardized protocol for pain and sedation management may help to lower the incidence of under- or over-estimating necessary pain treatment for infants. Protocolized sedation has been proven to improve the clinical outcome for critically ill adults (Curley, 2015), but it has yet to be proven for infants.
Because a team of caretakers is in charge of pain and sedation management in intensive care, doctors, nurses, and even pharmacists must work together to provide the best treatment (Curley, 2015). A widely used protocol could be put in place, providing less deviation in medication choice and dosage, allowing for a less varied outcome.

**Short-Term and Long-Term Consequences**

So far, much of the literature on the short-term and long-term effects of prolonged sedation with opioids and benzodiazepines is focused on premature neonates. Preterm infants in neonatal intensive care units (NICUs) often repeatedly experience painful procedures. Several studies have started to question and test the efficacy of sedative treatment.

Short-term consequences, as opposed to long-term sequelae, have been better studied. The effects (tolerance, dependence, and withdrawal) of prolonged opioid and benzodiazepine use can be seen before the infant is discharged from the hospital. Some of these adverse effects may be unavoidable, but at some point the risks of pain and sedation treatment may outweigh the benefits. Maybe the possibility of withdrawal could be lessened or altogether avoid by reducing the amount of sedation medications administered to an infant.
In order to monitor withdrawal syndrome in infants and children, withdrawal assessment tool-1 (WAT-1) can be used. Withdrawal syndrome occurs when a critically ill patient that has received prolonged sedation is either suddenly removed from or too rapidly weaned off the drug (Curley et al., 2012). Length of time and total opioid and benzodiazepine exposure influence the severity and rate of weaning. Over 50% of patients in the pediatric intensive care unit (PICU) suffer from iatrogenic withdrawal after 5 days of continuous drug infusion (Curley, 2013). Since iatrogenic withdrawal is a common, clinically significant side effect of prolonged sedation exposure, having a tool to assess the signs and symptoms for infants can greatly increase the clinical outcomes for these critically ill patients. The study showed that nurses were able to efficiently define and treat neonatal pain by using the WAT-1 (Curley et al., 2012), as shown in Figure 7.
FIGURE 7: Withdrawal Assessment Tool (WAT-1). Tool designed to be used twice a day to assess infant patient withdrawal. This rapid assessment can be easily used to provide decent accuracy, as opposed to other lengthier assessments. Figure taken from Curley et al., 2012.
Along with iatrogenic withdrawal, other sedation-related adverse effects may occur for infants in intensive care units. As always, there is the risk of undermanaging pain and sedation. Unplanned extubation or extubation failure were often experienced by younger patients, resulting in a longer hospital stay and an increased length of mechanical ventilation (Grant, 2013). In Grant’s study of sedation-related adverse effects (2013), adverse effects varied with the use of different sedation protocols. There is not currently a standardized treatment plan for pain and sedation management of critically ill infants. Many hospitals supply their physicians with their own recommended guidelines, making it difficult to compare protocols and determine which one is most effective. An example of sedation management guidelines is illustrated in Figure 8. Since these are recommendations, the team of physicians overseeing the critically ill patient ultimately designs the overall pain and sedation management, leading to variability in treatment in clinical outcome.
FIGURE 8: Boston Children’s Hospital Perioperative Pain Management Document From Patient Care Manual. These are the recommended guidelines for postoperative pain management - continuous infusions of opioids and benzodiazepines are suggested for prolonged sedation.
Undermanaging pain in infants is detrimental to the developing brain and nervous system, so pain and sedation management has the benefit of reducing the effects of chronic pain. The NEOPAIN trials (Anand, 2004) hypothesized that preemptive morphine would actually improve neurological outcomes in preterm neonates requiring mechanical ventilation. Although the study did not prove that pre-emptive morphine could decrease the occurrence of IVH, PVL, or death, the results did suggest that administering boluses of morphine were associated with a higher frequency of a positive outcome (Anand, 2004). These infants were not assessed after being discharged from the NICU, so long-term consequences were not able to be determined. The study conducted by de Graaf (2011) tested 5 year olds that had previously required mechanical ventilation as neonates and as infants were part of the trial on effects of morphine administration on pain and neurologic outcome. The children were tested on intelligence, behavior, hand-eye coordination, and health-related quality of life (de Graff et al., 2011). The results showed that short-term (5-7 days) morphine administration to preterm infants did not alter IQ, motor development, or behavioral problems at the age of 5. But in the IQ subtest for “visual analysis” there was a significant effect of morphine - children who had received morphine for their first 28 days obtained “visual analysis” low scores (de Graaf et al., 2011). This finding warrants a need for a future study or follow-up to test for alterations in neurocognitive functions. In a newer study performed by Ferguson (2012), preemptive analgesia in preterm neonates “did not have significant effects on IQ, academic achievement, self-
sufficiency, or motivational assessments at 5-7 years of age," echoing the results of de Graaf’s study. But Ferguson did find that head circumference and body weight were found to be decreased in the group of infants treated with morphine when compared to the control group (Ferguson, 2012). **Figure 9** displays the results of head circumference and body weight of the subjects in each treatment group, treated with either a placebo or morphine.
FIGURE 9: Head circumference and body weight results for each treatment group. Graph A shows the measurements of head circumference and graph B shows the body weight results. Circles indicate male subject and triangles indicate female subject. Figure from Ferguson, 2012.
Using parent-reported scores on behavior-rating scales, it was also apparent that the morphine treated group suffered more social problems, had decision response latencies when performing short-term memory tasks, and experienced differences in social interactions, suggesting long-term consequences (Ferguson, 2012). Although multiple study findings (de Graaf et al., 2011; Macgregor, 1998; Ferguson, 2012) have suggested that pre-emptive morphine administered to infants (particularly pre-term infants) does not lead to significant IQ deficits, the results of Ferguson’s study – decreased head circumference and body weight, response latencies, and differences in social interactions – suggest that there may be long-term consequences to early morphine exposure that we have yet to study.

There has also been increasing concern about the potential effects that prolonged pain and sedation medication exposure may have on the developing brain, since the brain is undergoing a significant amount of growth and development in the infant. After an increase in the number of neurons and synapses in the infant brain have reached an appropriate stage, there begins a decline in the number of neurons and synapses (Davidson and Flick, 2013). Neurons are removed via controlled cell death called apoptosis. Data from rodent studies have shown that a potential effect of analgesics may be accelerated apoptosis in the brain (Yon, 2005; Davidson and Flick, 2013). The effects of analgesics on apoptosis depend on age, length, and dose of sedation exposure.
Prolonged continuous exposure and repeated exposure may also increase the frequency of adverse effects (Davidson and Flick, 2013). These changes in brain development may lead to permanent brain modifications, resulting in future long-term consequences.

Studies have begun to turn to longitudinal studies in order to get a better look at possible long-term consequences for infants with prolonged morphine exposure. Magnetic resonance imaging (MRI) provides a noninvasive way to study the structural and functional differences of the infant brain (Dean et al., 2013). While this is a great tool to use in hopes of being able to predict long-term consequences prior to clinical symptoms, MRI of infants and young children may prove difficult since a clear MRI for this kind of study requires a patient to remain still without the use of sedatives for a period of time – a task difficult for children. Due to the rapid brain growth and development of infants, MRI scans would prove most useful if they could be taken before sedation exposure, during the period of sedation exposure, and after prolonged sedation exposure. This would allow for a baseline view of what the structure and function of the brain was like before exposure to any pain or sedation medication (Dean et al., 2013). Longitudinal studies like this can be challenging since many parents will not MRI scan their children prior to a medical condition and may not re-scan children once they have been treated and left the hospital. Figure 10 shows what a typical MRI

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scan would look like. To lessen the child's movements and increase the quality of the image, MRI scans were performed during natural sleep (Dean et al., 2013).

**FIGURE 10: Representative anatomical image and derived brain maps.** These images depict the typical quality of a child's MRI scan. This scan in particular was acquired from a 21-month-old patient. Figure taken from Dean et al., 2013.
Many of the studies that have put a focus on determining possible short-term and long-term sequelae of prolonged sedation exposure have used preterm neonates as their population of study. This is because preterm babies (born less than 37 weeks gestational age) often have many health issues requiring mechanical ventilation or surgical procedures, therefore leading to the necessary treatment with pain and sedation medications. A study performed on very preterm infants (born less than 30 weeks gestational age) showed that low-dose morphine exposure during care in the NICU was associated with altered cerebral structure, such as smaller brain volumes, and neurobehavioral issues (Steinhorn et al., 2015). But after follow-up at ages 2 and 7 years old, it was found that these problems did not persist; morphine exposed infants showed no significant difference in behavior once they progressed into later childhood (Steinhorn et al., 2015). But long-term effects may include a permanent alteration in sensory processing and future pain responses (Walker, 2009). These effects include differences in heat and mechanical sensitivity such as decreased thermal sensitivity in areas near scars, possibly due to localized tissue injury (Walker, 2009).

Overall, infants are at high risk of possible short-term and long-term sequelae due to prolonged sedation exposure because their brains and immature nervous systems are at a particularly vulnerable stage of development. Preterm babies are at even higher risk since they often suffer from health issues and medical
conditions that may require long durations of mechanical ventilation or repeated surgical procedures, both resulting in pain and sedation management with the use of opioids and benzodiazepines. Infants with the longest or highest total dose of sedation exposure are also at risk. The frequency and severity of adverse effects are influenced by the age at which the neonate is exposed stress and pain and to sedation medication, the amount of medication used, the length of exposure, and repeated exposure.
DISCUSSION

Data suggests that treatment with opioids and benzodiazepines can improve clinical outcomes by reducing pain and stress. We know that chronic untreated pain leads to adverse effects such as increased heart and respiratory rates, fluctuations in intracranial pressure, and increased stress hormone levels. These could lead to further complications such as IVH, PVL, or even death. So pain and sedation management is an important part of treatment in order to prevent these effects of undermanaged pain. But it needs to be taken into careful consideration that the sedation exposure may at some point become more detrimental than beneficial for the infant being treated.

Since infants treated in the NICU and PICU do not have a uniform, standardized treatment plan, recommended guidelines are followed by physicians. But this can lead to variations in pain and sedation management, as well as different clinical outcomes. Large doses of opioids and benzodiazepines are being administered to infants for extended periods of time, leaving these neonates at risk of not only short-term but also long-term sequelae. The preterm infant population is particularly vulnerable, since their brains are still rapidly developing and there susceptible to neurological effects of the sedation medications (Anand et al., 2010). Although undermanaged pain has its consequences, overestimating pain and administering excessive sedation medication may prove to be equally risky. Iatrogenic withdrawal is a common side effect of prolonged sedation, as well as
altered brain and nervous system development. After extended opioid exposure, infants may develop tolerance and dependence and suffer from hyperalgesia and withdrawal. **Figure 11** illustrates the diminished effects of opioid treatment.

**FIGURE 11: Clinical signs of diminished opioid analgesia.** Decreased effectiveness of opioid analgesic may be due to tolerance, hyperalgesia, and/or worsening pain state. Figure taken from Anand et al., 2010.

Opioid tolerance can be predicted by the total duration of opioid exposure. Tolerance rarely occurs after treatment of less than 72 hours (Anand et al, 2010). 35% - 57% of patients in the PICU often develop opioid tolerance, resulting in a longer hospital stay or further health complications (Katz et al., 1994). A study found that opioid withdrawal occurred in 100% of patients under 2 years old who were treated with continuous fentanyl infusions for 9 or more days (Katz et al., 1994). Signs of withdrawal include agitation, tremors, grimacing, sweating,
hypertensions, fever, vomiting, and diarrhea. In hopes of reducing tolerance and withdrawal symptoms, practical approaches could be used. Procedural changes such as interruption of the continuous infusion or sedative could be implemented (Anand et al., 2010).

The introduction of the MRI has really allowed for doctors and researchers to study the function and structure of the brain in a noninvasive manner (Raschle, 2012). Although it is difficult to scan an infant or child, seeing as they need to be motionless and not anaesthetized, the study of these scan could help us discover what, if any, consequences sedation exposure may have on the developing brain. Ideally, taking MRI scans before any sedation medication has been administered and then taking additional scans as the treatment is underway and after treatment has halted would be a great way to see the effects that the pain and sedation management have caused. Functional MRI could be used to monitor the effects that noxious stimuli may have on the developing brain (Hohmeister, 2010).

Overall, prolonged sedation exposure has been shown to result in short-term effects that may or may not lead to long-term consequences. But infants are still at risk for long-term sequelae. Studies have begun to suggest that intelligence and brain volume as well as head circumference may be altered by extended sedation exposure (Ferguson, 2012). Guidelines and studies on medication,
dosage, and duration need to be further investigated in order for patients in the NICU and PICU to have the most effective treatment. Physicians have overcome the issue of undermanaging infant pain, but there is still the issue of overestimating pain and administering unnecessarily high dosages or extended durations of sedation medications.
FUTURE STUDIES

This literature review suggests that infants, particularly preterm infants, are at high risk for developing short-term and long-term sequelae from prolonged sedation exposure. Future research is necessary to determine what the scope of long-term effects could be. This could include longitudinal studies that may involve the use of MRI scans and studies on the structure and function of the developing infant brain. Since there have been pilot studies indicating that prolonged sedation exposure may pose a long-term risk of intelligence deficits (de Graaf et al., 2011), more effective measures to quantify intelligence and behavior could be developed to help provide better understanding of possible neurological consequences.

Studying MRI scans taken of infant brains could also shed new light on developing brains and alterations influenced by exposure to sedation medication. Future studies on brain resting state networks using MRI and functional MRI (a sister technique to MRI that creates images of the brain based on metabolic function) may give us valuable new knowledge.

Because there is currently no standardized guideline for pain and sedation management, there is great variability in treatment and drug administration. New assessment techniques could be used in accurately determining how much stress or pain an infant is feeling. Development and implementation of a
nationwide guideline for pain and sedation management in the NICU and PICU could be effective in treating patients and obtaining a higher frequency of positive clinical outcomes. By effectively treating patients, withdrawal symptoms could be lessened, weaning off of drugs could decrease in duration, and risk of short-term and long-term consequences could be diminished.
REFERENCES


VITA

TIFFANIE LIU

Born in 1992
11 Worcester Street, Boston MA 02118
(814) 730-4367
TLIU814@gmail.com

EDUCATION

BOSTON UNIVERSITY, 2014 - 2016
Master of Science in Medical Sciences

STATE UNIVERSITY OF NEW YORK, UNIVERSITY AT BUFFALO, 2010 - 2014
Bachelor of Science in Biological Sciences

RESEARCH EXPERIENCE

RESEARCH ASSISTANT, 2015 – 2016
Boston Children’s Hospital – PAIN Group, Department of Anesthesia, Boston MA

I work as a research assistant for Dr. Dusica Bajic in the department of anesthesia at Boston Children’s Hospital (BCH). Our lab is part of a bigger PAIN group that involves projects and studies in ankle sprains, adolescent migraines, and brain resting-state networks. I specifically work on a project focusing on neonates with long-term exposure to opioids and benzodiazepines. I am responsible for a retrospective analysis of patients at BCH that have undergone prolonged drug exposure. I am also involved in a newer study, recruiting these same neonates in hopes of being able to study their resting-state networks through fMRI analysis. I have learned so much about lab funding, study recruitment, data analysis, and journal publications.

INTERN & RESEARCH ASSISTANT, 2012
DENT Institute – Neurological Center, Buffalo NY

The DENT Institute is a privately owned group practice for neurological specialties. I interned and performed research under Dr. Horatio Capote, a psychiatrist at DENT. I mainly worked with patients involved in a clinical trial that aimed to medicate patients with schizophrenia who did not have positive results to the currently approved medications or dosages. It was my first experience with research and I learned how to recruit patients, conduct a single-blind study, and analyze results.

WORK EXPERIENCE

SHADOWING, 2015 – 2016
Beth Israel Deaconess Medical Center - Podiatry, Boston MA
I currently shadow Dr. Kevin Riemer, a podiatric surgeon who specializes in at Beth Israel Deaconess Medical Center. He is an instructor in surgery at Harvard Medical School and he specializes in sports medicine, diabetic limb salvage, and repetitive stress injuries. I have been able to see pre-operative appointments, where patients have been referred to Dr. Riemer through specialists or their primary care physicians. I have also been able to see post-operative appointments after surgery or for additional care.

TEACHING ASSISTANT, 2014  
**SUNY University at Buffalo**, Buffalo NY

I was a teaching assistant for Dr. Joyce Sirianni’s Comparative Primate Anatomy class taught at the University at Buffalo. Comparative Primate Anatomy is a basic primate gross anatomy course involving the comparison of the human and primate anatomies. As a teaching assistant in the lab, I was responsible for the proper dissection of the human cadaver that would be used as a learning tool for the students. I would also have to prepare notes and drawings in order to better help students learn the material and dissect their own rhesus macaques. The hands-on style of teaching was a great learning experience for me.

**Sweet Home Family Medicine**, Buffalo NY

Sweet Home Family Medicine is a private group practice owned by Dr. Joshua Usen. His practice focuses on family medicine, medical aesthetics, and weight and wellness. I was hired as a secretary for the general practice and as a technician for an aesthetic treatment called Vaser Shape, a non-surgical cellulite and fat reduction treatment. In between appointments, I interned with Dr. Usen, shadowing him or one of his physician assistants. Working with Dr. Usen was a great opportunity; I learned about the importance of having a good primary care provider, discovered the cosmetic side of medicine (Vaser Shape, botox, and facial treatments), and gained secretarial and management skills.

SURGICAL INTERN, 2012  
**Pine Grove Ambulatory Center**, Warren PA

Pine Grove Ambulatory Center is an outpatient surgical center. I had the wonderful opportunity of being a surgical intern where I was able to stand-in on many different surgeries (colonoscopy, tonsillectomy, cholecystectomy, heel spur and bunion removal surgeries, cataract surgery, etc.). I learned a lot from each surgeon I worked with; they were great at educating me about their specialties and answering all of my questions. I was particularly in learning about the foot surgeries and the cataract removals.

**VOLUNTEER SERVICE**

TEACHER FOR ENGLISH FOR SPEAKERS OF OTHER LANGUAGES, 2015 - 2016  
**Rosie’s Place**, Boston MA
I currently volunteer at Rosie’s Place. Rosie’s place is primarily a daytime shelter that works to help and serve homeless women in the Boston area. I was originally involved as a volunteer in their food services and activities such as arts and tutoring. I was then offered a teaching position and I started in February 2015 as a teacher for English for Speakers of Other Languages (ESOL). It has been a wonderful learning experience so far, for both my students and me!

MEDICAL TRIP, 2013
VIDA Volunteer, Costa Rica and Nicaragua

Through the VIDA Volunteer organization, I was able to go on a medical mission trip to Costa Rica and Nicaragua. I was taught how to communicate with patients in Spanish and diagnose some of their issues without the use of the latest modern technology that is readily available to those in more developed countries such as the US and Canada. It was amazing to see how the healthcare system worked and differed in another part of the world, yet the goals and values of the doctors and nurses remained the same. The people I met and worked with – doctors, nurses, translators, and other students – were all beautifully intelligent people.

EMERGENCY DEPARTMENT VOLUNTEER, 2010 – 2011
Kenmore Mercy Hospital, Buffalo NY

I volunteered at Kenmore Mercy Hospital, mainly in the emergency department. I was responsible for checking patients in, helping nurses transport patients throughout the hospital, and communicating with patients, family, or friends in the waiting room. I was able to shadow the trauma surgeon a few times. Kenmore Mercy Hospital is not a big hospital so it was a great first experience for me; the doctors and nurses were so kind and they were able to offer me many opportunities to shadow and learn from them, as I was one of only a dozen volunteers.

AWARDS AND ACCOMPLISHMENTS

POSTER PRESENTATION, 2016
New England Science Symposium, Boston MA

POSTER PRESENTATION, 2015
Harvard Medical School Annual Poster Presentation, Boston MA

PROVOST SCHOLARSHIP, 2010 – 2014
SUNY University at Buffalo, Buffalo NY

At the University at Buffalo, I was granted the Provost Scholarship through the university’s honors college. The Provost Scholarship paid for $12,000 of my school tuition each of my four years. It was a great help in keeping my undergraduate costs low, as it paid for most of