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## **An Examination of the Long Term Effects of Exposure to Prescription Drugs on Infant Growth and Development**

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AN EXAMINATION OF THE LONG TERM EFFECTS OF EXPOSURE TO  
PRESCRIPTION DRUGS ON INFANT GROWTH AND DEVELOPMENT

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A Thesis Submitted to the Graduate Faculty of  
GRAND VALLEY STATE UNIVERSITY

In

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## Abstract

The effects of prenatal exposure to many prescription medications are well known. However, little is known about the long term side effects early exposure to medications used to treat pain and sedate have on growth and development. This paper explores the long-term effects of postnatal exposure to prescription medication. The potential effects are applied to physical, cognitive, and social-emotional development as well as the overall health of an infant. Additionally, the options of the use of commonly used analgesics and sedatives are compared to other pain management options. Research surrounding long-term effects of early exposure to pain and generalizations/recommendations are explained.

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## **Chapter One: Introduction**

### **Problem Statement**

Many reasons exist for infants to be hospitalized after birth. During a hospital stay, infants can receive a myriad of medications ranging from Tylenol to Morphine. Some of the drugs that are given to infants are those that are also given to adults. These prescription drugs are approved for use, so there is no question as to whether the drugs are effective. However, one question that still remains is: how does exposure to prescription drugs such as morphine or valium during infancy effect growth and development of the child? Growth and development of a child covers many areas. The intent of this thesis is to determine the effects of prescription drugs, if any, on cognitive, physical, social-emotional development as well as development of overall health.

In some cases, infants are diagnosed with neonatal abstinence syndrome (NAS). “Two major types of neonatal abstinence syndrome are recognized: neonatal abstinence syndrome due to prenatal or maternal use of substances that result in withdrawal symptoms in the newborn and postnatal neonatal abstinence syndrome secondary to discontinuation of medications such as fentanyl or morphine used for pain in the newborn” (Hamdan, 2012, para. 1). A diagnosis of NAS can include a variety of complications in behavioral and physiological development.

### **Importance of the Problem and Rationale for the Study**

The first four years of development are some of the most important in a person’s life in terms of development. What happens to a child’s growth and development if there is an interruption in typical development? For example, infants who are hospitalized and exposed

to prescription drugs may also experience a disruption in their physical development due to the hospital stay. While some infants require further intervention to assist in their development, many do not. Not all infants show signs of delays right away, but what if there are issues down the road? The infant may grow into a toddler who appears to be typically developing. It is vital for the development of the child to be as informed as possible of potential long term effects of prescription drugs.

### **Background of the Problem**

There are instances when infants require medical procedures that would cause them pain. However, without the use of drugs such as morphine or fentanyl, the effects could be detrimental to the development of the infant. “The mounting of a surgical stress response results in catabolic responses, including glycogenolysis, gluconeogenesis and lipolysis during the perioperative period. These catabolic responses, when unmodulated by medical intervention, may have a detrimental effect on the clinical course of a neonatal surgical patient. Adverse circulatory and respiratory events are also more likely during the postoperative course of neonates who have had inadequate interventions to minimize stress response. These responses include tachycardia, systemic hypertension, pulmonary hypertension and neuronal excitotoxicity. Furthermore, inadequate treatment of pain in neonates may have implications that extend beyond the neonatal period, including long-lasting changes in pain behavior” (El Sayed, Taddio, Fallah, De Silva, & Moore, 2007, p. 444). Given the detrimental effects prolonged pain could cause, doctors and surgeons are left with no choice but to medicate even the youngest patients. One of the difficulties in this

situation is that most drugs are evaluated and approved for adults, not children, let alone infants.

Prescription drugs are commonly used in pediatrics for children aged between 0 and 18 years for the management of various disorders. “In the United States, pediatric patients, on average, visit a physician's office almost twice a year and marketed drugs are prescribed in up to 60% of these visits. Despite the therapeutic benefits of prescription drugs, their use can be associated with potentially serious side-effects. For example, a systematic review found that 9.5% of pediatric patients developed adverse drug reactions after receiving drug treatment during their hospital stays and 12% of these reactions were life threatening. Given the potential for serious harm that prescription drugs may cause, adequate assessments of drug safety in pediatrics have become central to the overall health of this vulnerable population” (Luo, Doherty, Cappelleri, & Frush, 2007, p. 2607). Although commonly used prescription drugs are not approved for use by pediatric patients, it does seem to be common practice.

Another difficulty that medical professionals face is the assessment of pain of an infant. Unlike older children and adults, infants cannot verbally express the pain they are in; therefore they have to rely on doctors, nurses, and family members to determine the level of pain of the infant. “In order to assess the effectiveness of medical therapy, pain must be able to be evaluated. However, there is no objective pain meter. The perception of pain includes a sensory component, involving neural pathway activation in response to noxious stimuli, and an effective response, which involves behavioral and cognitive factors” (Rosen & Dower, 2011, p. 245). Given that information, there are many pain scales used to measure a



patient's level of pain. Two common pain scales are the CHIPPS (Children's and Infants' Postoperative Pain Score) and CRIES (Crying, Requires Increased oxygen administration, Increased vital signs, Expression, Sleeplessness) (Gitto et al., 2011, p. 929). Each of these scales measure pain based on observations of adults rather than communication from the patient. As indicated in the full name of each scale, medical vital signs do play a role in pain assessment. Nurses and doctors monitor respiratory rate, heart rate, as well as facial expressions to determine whether or not a child is in pain. One issue with scales such as CHIPPS and CRIES is that they rely on observations, not self-report so the pain may be underestimated (Berde & Sethna, 2002). In order to meet the pain management needs of infants, medical professionals need to consult the family of the patient in addition to monitoring vital signs.

The research indicates that prolonged or even early exposure to pain could alter the nociceptive circuits (sensory neurons that communicate with the brain and spinal cord) in the brain, creating over or under reaction to pain. Research of specific drugs commonly used as analgesics or sedatives also provides information regarding potential harmful side effects. This information places medical professionals and families in a bind. Should the infant be untreated and therefore exposed to the potentially harmful effects of pain? Or, should the infant be medicated and exposed to the potential side effects of drugs, or the potential of being over medicated unnecessarily? This is the predicament that must be dealt with when treating infants. The research states that an individual pain management plan should be created using both pharmacological intervention as well as non-pharmacological strategies. "Optimal pain management should include a combination of prevention, pharmacologic

strategies, and non-pharmacologic approaches, or some combination of these techniques” (Walter-Nicolet, Annequin, Biran, Mitanchez, & Tourniaire, 2010, p. 356).

There are several different non-pharmacological pain management strategies that have been found to be effective. “Non-pharmacologic treatments may be beneficial in many ways, including decreasing anxiety and reducing the need for opiates or other analgesics” (Rosen & Dower, 2011, p. 244). Several of the most common pain management strategies that do not include medication involve a family member. By involving the family, stress on the infant and family could be lowered. The most common non-pharmacological strategies are: kangaroo care (skin-to-skin contact), swaddling, non-nutritive sucking, rocking or holding, distraction through the use of toys, talking, or music. Infants can also be given a serum of glucose or sucrose. It is thought that the sweet taste has a psychological effect on the infant (Rokyta & Fricova, 2012). All of these strategies reduce the pain the infant feels during a painful procedure like a heel prick. However, for infants who have chronic or post-operative pain, a combination of pain management strategies is most likely needed.

Additionally, hospitals typically have a team in place to assist children and families with decisions about creating pain management plan, reducing anxiety, and providing opportunities to participate in various activities. Child Life Specialists assist the patient by providing medical play opportunities to ease anxiety surrounding medical procedures as well as art and music therapy to distract patients and ease pain (Regents of the University of Michigan, 2013).

When it comes to pain management for infants, analgesics and sedatives are often necessary in order to keep the infant comfortable. While non-pharmacological strategies do

alleviate pain or distract the patient, pharmacological intervention is often a necessity (Tobias, 2005). Drugs that are commonly used to treat infants can be broken into a few categories based on the way they work. The World Health Organization (WHO) has created lists of the most commonly used drugs in each category. Opioids are probably the most well known drugs used as analgesics. This category contains morphine, fentanyl, and methadone. Not only are opioids the best known category, they have also been studied the most, and therefore are considered tried and true. Opioids impact the central nervous system which makes them a drug of choice for moderate to severe pain. Benzodiazepines are another category of drugs used for pain management in infants. The two most common benzodiazepines are Midazolam and Lorazepam. This category of drugs depresses the central nervous system, allowing the infant to become relaxed and possibly drowsy. Barbiturates are yet another category of drugs proven to alleviate pain. The most common drugs in this category are Phenobarbital, Thiopental, and Ketamine. Ketamine, most commonly used in the NICU/PICU. Barbiturates affect the body by depressing nerve activity in large muscle groups of the body. Given the potential for dependency and unpredictability of patient reactions, barbiturates are not the first choice for pain management in infants. Finally, non-steroidal anti-inflammatory drugs (NSAIDs) are the final choice for pain management. The most common NSAIDs are Acetaminophen, Ibuprofen, Naproxen, and Ketorolac. “NSAIDs have well known analgesic, antipyretic and anti-inflammatory effects (Gazarian & Graudins, 2006, p. 71). While all of these drugs have been found to be effective in pain management for infants, many are still being used “off-label” as their effects on infants and children have not been studied.

There appears to be a gap in knowledge and research regarding the effects of prescription medication on pediatric patients. This gap includes current studies of short term and long term effects on children. “Over the last decades, it was believed there was a need to protect children against research. There is now an increasing notion that they also have a right to benefit from research that keeping them systematically out of the research process amounts to withholding from them the potential benefits of pharmaceutical progress, and that exposing them continuously in daily practice to medicines not properly tested in their age group is ethically challenging. This has led to the new paradigm that children need protection through, not against, research and clinical trials” (Rose, 2009, p. 57). A shift in thinking of clinical drug trials may give way to accurate information about the effects prescription drugs have on pediatric patients. How does this shift affect regulations and approval by the Food and Drug Administration?

### **Statement of Purpose**

Although the medical and pharmaceutical communities are changing, a gap still remains in research involving prescription drug use among pediatric patients. The purpose of this study is to review and analyze current research on the effects of prescription drugs have on human growth and development. Upon analyzing current research, a qualitative report will be completed detailing findings in the areas of cognitive, physical, and social-emotional development. Additionally, effects of prescription drugs on the overall growth and health of a person who was exposed to prescription drugs in infancy. Once the findings have been analyzed and reported, any trends or gaps in research will be added to the study. Finally, areas and suggestions for further research will be discussed.

## **Research Questions**

While the focus of this study will be the long term effects of prescription drugs on human growth and development, many other questions have arisen. As previously stated, growth and development covers an array of areas. One area that may be affected is nutrition. Does exposure to prescription drugs in infancy affect the overall nutrition of the infant? Are they able to eat and therefore grow at a similar rate to those infants who were not exposed to such drugs? Also, how does the hospitalization itself contribute to the infant's growth and development? Assuming that these questions can be answered with current research, an additional question would be, how does or can the Food and Drug Administration use this information?

## **Design, Data Collection, and Analysis**

Through documentary research, a qualitative report will be written. As previously stated, current research will be reviewed and analyzed. In order for research to be considered current, it will have been published within the last decade. Any research reviewed and analyzed with a publication date older than ten years had no conflicting research with a more recent publication date. The literature that will be used in the study will be journal articles that have been peer reviewed. Analysis of the literature will consist of determining the most commonly used analgesics and sedatives in Neonatal Intensive Care Units. Additionally, side effects of the most common drugs will be determined and applied to various stages of development. The focus will be in the areas of cognitive, physical, and social-emotional development. Effects of prescription drugs on the overall growth and health of a person who was exposed to prescription drugs in infancy will also be discussed. Any additional research

questions that can be answered will be incorporated into the findings or documented as an area for future research. Trends and or gaps in research will also be included in the study. Lastly, areas and suggestions for further research will be discussed.

### **Definition of Terms**

Analgesic - Drug that relieves pain without impairing function (Merriam-Webster, 2013).

FDA - Food and Drug Administration

NICU - Neonatal Intensive Care Unit

NSAIDs - Non Steroidal Anti Inflammatory Drug

Sedative – Drug that helps calm (Merriam-Webster, 2013).

WHO - World Health Organization

### **Organization of Thesis**

Chapter Two contains a literature review on the topics of pain, pain management, drug development and use, and details of effects on development. This leads into Chapter Three which summarizes the literature review as well as details the research process. Chapter Four contains the main findings of the study, including areas for further research. Finally, Chapter Five is a summary of the entire thesis.

## **Chapter Two: Literature Review**

### **Introduction**

This chapter includes a discussion of the difficulties in determining the long term effects of exposure to prescription medication in infancy. The chapter begins with an explanation of how the Food and Drug Administration plays a role in which medications are approved for use in infants, children, and adults. In addition, there is information regarding the use of such medications whether they have been approved for use on children and infants and the reasons why. This leads into the dilemma of whether or not to medicate children and infants with unapproved medication or allow them to potentially suffer long term effects of exposure to pain. Ultimately, the pros and cons of pain management through the use of analgesics and allowing an infant to be in pain are detailed. Additionally, the efficacy and side effects of the most commonly used drugs are discussed. Finally, typical infant development is discussed and compared to development of an infant who was exposed to drugs and how they may develop. Suggestions to support development are also included.

### **Theoretical Framework**

There are many reasons for adults and children alike to be hospitalized. During a hospital stay one would expect to receive some type of medication. Most people seem to know that adult medications cannot usually be given to children, particularly infants. However, it was not until 1992 that the Food and Drug Administration (FDA) began to regulate the use of medications on pediatric patients (Buck, 2000, p. 95). The first regulation of pediatric medications spurred other regulations that provided for pharmacological studies on pediatric patients. From those regulations came more accurate labeling of drugs and the

development of pediatric pharmacology units (Buck, 2000). Subsequently with all of the progress in medication labeling and dosing the need emerged for longitudinal studies of potential side effects and/or long term effects of such drugs. However, the administration of drugs to pediatric patients has not changed greatly as most medications approved for pediatric use are drugs that are rarely used on pediatric patients. Additionally, those drugs that are commonly used for pediatric patients are not generally used for pediatric studies and therefore not approved for pediatric use (Boots et al., 2007). The following chapter will discuss additional FDA regulations in regards to pediatric patients, the balance between long term effects of exposure to pain versus long term effects of exposure to prescription medication, and any known long term effects of pain or medication exposure.

## **Synthesis of Research Literature**

### **Role of Food and Drug Administration**

Infants who survive traumatic events sometimes show signs of developmental delays in several areas of development. The actual hospital stay and procedures are usually the reason assumed for the delay in motor, cognitive, or nutritional development. However, lasting effects of medications are not typically discussed. If infants and children are given medication to which some adults develop a dependency or addiction, what about the long term effects the same medication could have on the development of a child?

As important as knowing long term effects of medications are, longitudinal studies involving pediatric patients are nearly non-existent. In the past few decades, the Food and Drug Administration has passed several regulations involving medications for pediatric patients. However, there are still several reasons why there are very few longitudinal drug



studies of pediatric patients. “Before regulatory approval, all prescription drugs must go through rigorously designed pre-marketing randomized clinical trials (RCTs) to ensure efficacy and safety. Unfortunately, only about 20% of the drugs used to treat pediatric patients in hospitals or in general practice have gained regulatory approval for pediatric use. The other 80% either do not have an approved indication for pediatric use or are prescribed outside of product label (‘off label’). The safety of using these drugs in the pediatric population has not been well tested by pre-marketing RCTs and, consequently, little is known about the potential side-effects that these drugs may cause to pediatric patients” (Luo et al., 2007, p. 2608). It is a concern that there is little information regarding side-effects and long term effects of prescription medication taken by infants and children.

### **Long Term Effects of Pain versus Effective Pain Management**

“Pain produces suffering, fear, and vital inhibition. As individuals, we have a strong urge to minimize the risk for and the suffering from pain. Therefore, moderate and severe postoperative pain can and should be prevented or controlled safely and effectively in all children whatever their age, severity of illness, or surgical procedures” (Messerer, Gutmann, Weinberg, & Sandener-Kiesling, 2010, p. 879). Anyone who has undergone a surgical procedure expects to feel some pain. However, adults and older children can describe the feeling and location of the pain. Infants are different. “Another problematic aspect about pain in children is the lack of a clear understanding about how children at different stages of development may respond to pain (Turkoski, 2007, p. 194). Infants of all ages do communicate to us, but often times their signals go unnoticed or are misread. “A gathering body of animal and human evidence suggests that early pain has long-term consequences on

the developing individual” (Ponder, 2002, p. 218). So again, the dilemma is deciding between pain management and prescription drugs with potentially life altering side-effects.

“Chronic pain in children has a negative impact on the quality of life, resulting in social and emotional consequences for both the child and the family (Messerer et al., 2010, p. 879). Children and infants who are in pain are often given an opioid to relieve their pain. However, as previously mentioned, long term effects of prescription drug exposure has not been widely studied. For the purpose of this study, only the most common types of analgesics and sedatives will be discussed.

### **Effects of Pain versus Effects of Prescription Pain Medication**

As previously discussed, there could be negative long term effects from exposure to pain and prescription medications during infancy. As a family member or medical professional, weighing the options for an infant would be difficult. There are pain management options that provide the best of both worlds, less pain medication and less pain.

As mentioned in chapter one, there are pharmacological interventions as well as non-pharmacological strategies to lessen the pain an infant endures. “Pain has been shown to evoke specific brain activity in the cerebral cortex starting at 24 weeks of gestation. Of special concern is that this time period includes several critical developmental stages and plasticity of certain nociceptive circuits can create long-term changes. Early experiences with pain during these critical periods can be reflected in pain perception in adulthood. Therefore, the period in which pain exposure begins is very important” (Rokyta & Fricova, 2012, p. 110). Knowing that early exposure to pain is key in the alteration of pain recognition, medication seems to be a necessary component of pain management. None of

the non-pharmacological strategies have been proven to completely alleviate pain, only lessen through distraction.

As a parent of an infant in pain, the decisions regarding the best treatment for your child are difficult to make and rely heavily on medical staff and their knowledge. It is safe to assume that no parents want to see their child in pain. When it is necessary, infants are given drugs that are typically reserved for adults. However, with the alleviation of pain could come with some costs. All medications have side effects of one sort or another. The most common pain management drugs are opioids. Along with opioids, benzodiazepines, barbiturates, and NSAIDs are commonly prescribed as part of a pain management plan. All of those drugs have potentially detrimental side effects. One side effect that all of these drugs have in common is the potential for overuse. As previously mentioned, there is not an objective way to assess pain that infants feel, as they cannot communicate verbally. With that said the determination of when to administer a dose of medication is at the discretion of medical staff. Additionally, the majority of these drugs are used “off-label,” which means they have not been approved by the FDA for use on children. In the case of “off-label” use, improper dosing is a concern, as there is no dosing information for children. Another common issue with the use of any of the above categories of drugs is the potential for interaction with other medications the infant may be given. Along the same line, specific drugs must be avoided given the diagnosis of the patient. Many drugs are not suitable for specific conditions.

Each of the drug categories has its own unique list of potential side effects. Keep in mind that these are side effects known for use of the medication in adults, the effects on infants and children could be different.

Opioids: respiratory depression, nausea, vomiting, constipation, drowsiness, dizziness, pruritis, muscle spasms, and urinary retention

Benzodiazepines: physical dependence, drowsiness, over-sedation, myoclonic jerking, and respiratory depression.

Barbiturates: physical dependence, sedation, altered mood and behavior.

NSAIDs: adverse effects on the hepatic system, nausea, diarrhea, gastrointestinal ulceration and bleeding, headaches, dizziness, fluid retention, and rashes.

(WHO, 2010) (Scottish Neonatal and Paediatric Pharmacists Group, 2010)

### **Most Common Pain Management Drugs**

**Opioids.** “Opioids are widely used for analgesia and sedation in neonates. They have potent analgesic effects, sedative but no amnesic or hypnotic effects, weak to moderate effects on hemodynamic stability, and reversible adverse effects. Their adverse effects include respiratory depression, bronchospasm, reduced gastrointestinal motility, urinary retention, and pruritus” (Walter-Nicolet et al., 2010, p. 358). There are many types of opioids used for pain management; this study will discuss only the most common types of opioids.

“Morphine and fentanyl are the most commonly used opioids in the NICU” (Walter-Nicolet et al., 2010, p. 358). Since morphine and fentanyl are the most commonly used opioids for pain management of neonates, there should be longitudinal studies of the long

term effects. However, there are very few studies of long term effects of either of these medications. The majority of side-effects previously mentioned are short term effects. Additionally, the majority of longitudinal studies that were found were conducted on preterm infants, not full term infants. This poses a problem, as preterm infants may have other factors that affect their development aside from effects of medications.

**Benzodiazepines.** “The benzodiazepines are anxiolytic drugs that have limited analgesic effect but are commonly used in NICU’s to produce sedation, muscle relaxation and provide amnesia (in older patients)” (Hall & Shbarou, 2009, p. 17). There is limited research regarding the analgesic properties of benzodiazepines, but they are still a drug of choice for pain management in infants. There are two commonly used benzodiazepines for pain management of infants, midazolam and lorazepam. Typically, both midazolam and lorazepam are used in combination with morphine to better control pain and provide more effective sedation. While benzodiazepines are used in the NICU, they can have significant side effects, the most common in myoclonic jerking, which is similar to convulsions created in seizures. Additionally, benzodiazepines have the potential to cause respiratory depression, excessive sedation, and at times hypotension (Hall & Shbarou, 2009).

**Barbiturates.** “Barbiturates are commonly used in neonates for sedation and analgesic effects, despite a lack of evidence for pain relief” (Hall & Shbarou, 2009, p. 18). The most common barbiturate is phenobarbital. Phenobarbital is widely known as a drug for seizure control. However, there is evidence in animal studies of its analgesic properties. Although there are animal studies indicating analgesic effects, there have been no studies in regards to use with infants. Phenobarbital can cause some adverse reactions, most

commonly, sedation, depression, insomnia, and altered mood or behavior. In addition to the above side effects, there is the chance of physical dependence and severe adverse reactions with many other commonly used drugs (WHO, 2010).

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).** “NSAIDs are effective in alleviating pain and inflammation in infants and children. They are generally well tolerated when used for appropriate indications, in recommended paediatric doses, and with consideration of relevant precautions” (Gazarian & Graudins, 2006, p. 71). NSAIDs are unlike many of the other drugs previously discussed; some can be purchased over the counter and used without a prescription. While NSAIDs are widely used, they do not offer the same analgesic effects as opioids. In fact, the analgesic ability of NSAIDs has not been studied for use in neonates. NSAIDs tend to take longer to take effect, last for a shorter duration, and generally require higher doses than other analgesics (Gazarian & Graudins, 2006). As with all other medication, there can be adverse effects. The most common side effects are adverse effects on the hepatic system, nausea, diarrhea, gastrointestinal ulceration and bleeding, headaches, dizziness, fluid retention, and rashes. Although it is assumed that NSAIDs like ibuprofen have beneficial analgesic properties, some of the side effects have caused medical professionals to use NSAIDs cautiously.

**Other Commonly Used Drugs.** “Ketamine is a dissociative anesthetic used for anesthesia, analgesia and sedation” (Hall & Shbarou, 2009, p. 18). Although ketamine has several uses, it is typically given for short durations for painful procedures and as maintenance of anesthesia (WHO, 2010). Research indicates that the effects of ketamine are still under investigation. Several animal studies imply there are neurodegenerative effects

that could be caused by ketamine. However, there are no conclusive human studies indicating one way or another the effects ketamine has on the human brain (Hall & Shbarou, 2009). Even though some effects of ketamine are questionable, many are not. Ketamine has been shown to raise blood pressure and pulse rate, raise intracranial and intraocular pressure, hypersalivation, increase muscle tone, in some cases alter mood and behavior (WHO, 2010). The potential side effects of ketamine are what make its desired use short term. But, the anesthetic, analgesic, and sedative properties make it a drug of choice even for infants.

### **Developmental Domains**

Reasons for a hospital stay range from one day to many days. During that stay, the patient may be exposed to many different medications including analgesics and sedatives. Generally, a person is in the hospital to heal which requires rest. Imagine an infant “resting” as they heal. During the first year of life infants are supposed to be active and curious. The following sections detail three areas of development, physical, cognitive, and social-emotional.

**Physical Development.** Physical development requires movement and can be broken into two categories, fine motor and gross motor. Fine motor means, “using hands to be able to eat, draw, dress, play, write, and to do many other things” (Boyse, 2012, para. 2). For an infant, fine motor skills are developed through manipulating objects, reaching for objects, and interacting with family members. Gross motor involves, “using large groups of muscles to sit, stand, walk, run, etc., keeping balance, and changing positions” (Boyse, 2012, para. 2). Just as fine motor skills are developed through movement, so are gross motor skills.

**Cognitive Development.** Similarly to physical development, cognitive development depends on an infant interacting with their environment. Cognitive development refers to “thinking skills, including learning, understanding, problem-solving, reasoning, and remembering” (Boyse, 2012, para. 2). If an infant is sedated they are unable to interact with their environment, family, or medical staff. In terms of cognitive development, by one month of age an infant prefers to study human faces over other objects, can recognize the smell of mother’s breastmilk, and recognizes some sounds and may turn in that direction (American Academy of Pediatrics, 2013). By three months, a typically developing infant should be able to look in the direction of a familiar sound like a voice, recognize their bottle or breast, look in the direction of bright colors or lights, and respond to noise such as a rattle (American Academy of Pediatrics, 2013). By six months, an infant should be able to add to opening mouth for spoon and imitate familiar actions performed by caretakers (American Academy of Pediatrics, 2013). In the same way that physical development is structured, where each skill builds on the last, so is cognitive development. For example, if an infant is not responding to familiar voices and studying their caretakers, they will not be able to mimic familiar actions.

**Social-Emotional Development.** Social development and cognitive development are closely related, specifically in infancy. Social emotional development can be described as, “interacting with others, having relationships with family, friends, and teachers, cooperating, and responding to the feelings of others” (Boyse, 2012, para. 2). If an infant is sedated or constantly feeling ill from medications, interactions will be limited and therefore social emotional growth stunted. An infant who is one month of age typically prefers to study



faces, tend to enjoy soft touches, and recognize and respond to some sounds. By three months old, an infant generally calms when held or spoken to in a soft, familiar voice, communicate through cooing or gurgling, cry or change expression to indicate hunger, pain, or fear, and smile in response to others smiling. And, by the age of six months, an infant should be babbling, recognize familiar faces, smile at self in mirror, scream, laugh, and squeal (American Academy of Pediatrics, 2013). As with cognitive development, infants need to interact in order to develop socially and emotionally.

### **Summary**

Sitting by your child's bedside during a hospital stay can be daunting on its own. But, as you watch your child recover, you may begin to wonder about the effects of the drugs to which your child has been exposed. Fortunately, the Food and Drug Administration has begun to pass regulations that mandate labeling drugs for use in the care of infants and children. The FDA also passed regulations making it possible for drug studies on children. With the new regulations from the FDA, the hope is for more longitudinal studies on the effects of prescription medication.

### **Conclusion**

Although there have been many advances in the development and testing of drugs for children, there is still progress to be made. There are a limited number of longitudinal studies conducted on the effects of prescription drugs on infants and children. Recently, the FDA has passed regulations that open the door for drug studies to be conducted using children as subjects. This poses yet another issue in determining long term effects of prescription drugs; who is going to volunteer their child for a drug study?

The true long term effects of prescription drugs on children could also be difficult to determine. Children who require such medication also may have had a lengthy hospital delay due to an illness, surgery, or being born premature. All of these factors contribute to the difficulty of determining whether long term effects are due to exposure to medication or another factor.

## **Chapter Three: Research Design**

### **Introduction**

The purpose of this study is to discover what research says about the long-term effects of exposure to prescription medication during infancy. A thorough literature review was conducted. Through the literature review it was discovered that little is known about the long-term effects of prescription drugs on the development of an infant. Given that there is nearly no information regarding long-term effects, the study was refocused on short-term, physiological effects that impact development. From there, the most commonly used drugs in NICUs were identified. Once the drugs had been identified, the physiological effects were then identified. In order to analyze the effects of the most commonly used drugs, typical development in the first six months of life was researched. The impact of the most commonly used drugs were then applied to development in the first six months of life. Long-term effects were then related to the short-term effects on physiological development of an infant.

This chapter contains a discussion of instrumentation of the study. The first section explains the instrumentation. This is a qualitative study that was conducted through documentary research. Next, data collection is discussed. Finally, the chapter concludes with a presentation of data analysis.

### **Instrumentation**

A qualitative approach was deemed the most effective way to approach this study by gathering data through reviewing and analyzing current research. Through reading literature related to medications administered to infants, side effects of those medications and

developmental theory, it was possible to identify units for analysis which were used to compare across categories and discover relationships between drugs, physiological effects, and developmental milestones. This approach allowed for generation of hypotheses grounded in data that related to possible impacts of medications on critical developmental periods (Goetz & LeCompte, 1981). This was particularly important because little is known or documented in the research about the effects of medication on the development of infants. When completing qualitative research, the researcher generally observes, analyzes, and interprets the information. In this case, there was no setting in which to observe and analyze. Instead, documentary research was chosen. However, conducting the study through documentary research limits the study by reviewing, interpreting, and analyzing data collected by others.

The initial goal of this study was to determine what long-term effects, if any, are experienced by people who were exposed to medication in infancy. Little to no information was found regarding the long-term effects of exposure to prescription drugs on infant growth and development. At that point, the questions that guided the study were reframed. There are many drugs given to infants, so, in order to determine which medications to focus on, the drugs most commonly used in the NICU needed to be determined. This led to the two most common reasons infants are medicated, pain management and sedation. From there, the most commonly used analgesics and sedatives were determined. Additionally, the short term side effects of the most commonly used analgesics and sedatives were researched. The short term side effects were then applied to stages of infant growth and development so that connections

could be made to potential long term side effects. The majority of resources for this study are from medical journals.

Articles relating to full-term infants who were hospitalized and exposed to prescription medications were reviewed. The research focused on full-term infants based on the fact that pre-term infants could have other complications that would make it more difficult to determine whether long-term effects are from exposure to medication, hospitalization, or complications from prematurity.

Research also led to discovery of the Food and Drug Administration's role in the use of drugs on pediatric patients. From the information on the FDA came many other questions and articles; however, they strayed from the original research question and were ultimately dismissed.

There were some topics not included in the study, due to time constraints and depth of the study. Specific reasons for hospitalization were not considered as the symptoms or recovery could add to the complexity of determining long-term effects of medication. Medications that were excluded were those that are generally taken by adults and only administered to children in extreme circumstances. Additionally, medications that were discussed have the primary function of analgesia or sedative. There are many other medications used in NICUs that are not primarily used for analgesia or sedation.

### **Data Collection**

For the purpose of this study, data was collected through extensive literature review. The majority of sources for this study were found via the Grand Valley State University Library online system. Some of the search terms include: long-term effects of medications,

most commonly used medications in NICUs, side-effects of prescription medications, and infant development. Most of the sources relating to medication and side effects were published in medical journals found on Medline and ProQuest Medical Library. The majority of sources for information regarding specific medications and their side effects were published in medical journals. Most of the journal articles were reviewed by peers in the medical field. The information regarding child development was collected from websites dedicated to the health and development of children. The websites the articles were obtained from were supported by the American Academy of Pediatrics and the University of Michigan Health System. Both of these associations conduct research of their own. Each of the articles that were reviewed and cited contained specific information about adverse reactions of medications, growth and development of infants, information about the FDA and drug development, and specific medications.

The discovery of research began with searching for articles that contained information regarding long term effects of prescription medication on infant development. When no articles were found containing such information, the search was refocused on discovering the possible impact the most commonly used drugs could have on development. First, articles discussing the most commonly used drugs in Neonatal Intensive Care Units were gathered and analyzed to create a category. Next, articles detailing all known side effects of those drugs were gathered and analyzed, creating a new category. Finally, the third category was created with information about typical infant development in the first six

months of life. This category was created in order to apply short term side effects to the first six months of development. From there, hypotheses could be made regarding long- term effects of these medications on growth and development.

### **Data Analysis**

Data was collected through literature review. The literature review began with an internet search for long-term effects of prescription medications given to infants. After searching with multiple key words and no articles matching the criteria, it was determined that no information meeting the criteria exists. Given that no information could be found, research questions were refocused in order to determine from current information, the physiological, short-term side effects of the drugs, and identify relationships to their impact on development. Data was triangulated by using multiple sources of information, through extensive review of the research.

Data was analyzed using a constant comparative method (Glaser & Strauss, 1967). Units of analysis were defined. As data was collected, it was recorded, classified and compared across categories. Relationships across categories were identified. The first unit of analysis was defined as the names of drugs administered to infants. From that unit of analysis categories of the most commonly used drugs were identified. The second unit of analysis was defined as short-term side effects of the most commonly used drugs. The third unit of analysis was defined as developmental milestones during the first six months of life. These categories provided a framework for aligning the physiological effects of those drugs with physical, cognitive, and social-emotional domains of development.

The most commonly used drugs were identified by the frequency of specific drug names in conjunction with its use in NICUs in the literature. Each time a specific medication was mentioned, it was tallied. Additionally, several medications were mentioned in articles as being the most “commonly used” analgesic or sedative. After reviewing the literature and medication names, the medications most frequently mentioned were chosen for this study. The medications that were discussed most often were morphine, fentanyl, lorazepam, midazolam, Phenobarbital, ketamine, ibuprofen, and acetaminophen.

Once the most commonly used drugs were determined, the most common side effects were identified. A table was created with each drug and listed the known side-effects. The side-effect was marked each time it appeared in the literature. Again, the side effects with the most tallies were the side effects deemed most common. Side effects that were mentioned in one article or referred to in extreme cases were not considered common. Additionally, the most common side-effects were tracked and recorded in order to generalize potential long-term effects of prescription drugs.

In order to correlate potential side effects of medications to stages of development, developmental milestones were identified. The time frame for development was focused on the first six months of life. The reason for the time frame was based on exposure to medication occurring shortly after birth. Most likely, typical development would be delayed or interrupted during first six months due to hospitalization, therefore making the first six months of development the most effected time period of development. Research was reviewed from credible sources such as the University of Michigan and the American Academy of Pediatrics. After identifying physical, cognitive, and social-emotional



developmental milestones another table was created highlighting typical development. After researching developmental milestones, the short-term side effects were applied to stages of development. As the short-term side effects were applied, generalizations were made regarding potential long-term effects.

Upon researching short term side effects of the most commonly used drugs and stages of development, connections became apparent. Many of the short term side effects interrupt the process of typical development. If typical development is interrupted, then infants most likely would not meet developmental milestones as expected. Once connections could be made between known short term side effects and infant development, potential long term side effects could be predicted. From all of the research and connections that were made, ultimately, more questions arose.

### **Summary**

The goal of this study was to determine the long-term effects of exposure to prescription medication on infant development. After searching for information, with no success, the study was refocused. In order to infer long-term effects, short-term effects of the most commonly used drugs were applied to development in the first six months of life. Data for this study was collected through an extensive literature review. The data collected and analyzed was in the categories of most commonly used drugs, their side effects, and typical development in the first six months of life.

## **Chapter Four: Results**

This chapter begins with an explanation of the context of the study. Once the context of the study has been stated, the chapter moves on to discuss the findings of the study. Included in the findings are areas that need further study. Finally, the chapter concludes with a summary.

### **Context**

The context for this study is research literature. Data was gathered through the use of the internet use of the internet for articles listed in medical databases that contain peer reviewed journal articles. Documentary research was the best choice for this study based on the fact that actual field work could take decades to determine long-term effects of prescription drugs.

### **Findings**

The findings in this study are based on some very interesting data as well as implications for further study. The main question, the question that this study stemmed from, what are the long-term effects of exposure to prescription drugs during infancy? According to a review of the literature, the only effects that have been studied and documented are all short-term effects. Based on analysis of the data, the most commonly used analgesics and sedatives used in Neonatal Intensive Care Units can be classified as opioids, benzodiazepines, barbiturates, and non-steroidal anti-inflammatory drugs. Each category has its own drugs of choice for use in the NICU. The most commonly used opioids are morphine and fentanyl. Benzodiazepines most commonly used are midazolam and lorazepam. Phenobarbital is the most commonly used barbiturate. NSAIDs have two commonly used

medications ibuprofen, and acetaminophen. There is one other commonly used drug that does not fit into any of the categories. Ketamine is also used commonly used in NICUs. Table 1 contains the most common medications used in the NICU and their known side effects.

Table 1

<b>Drug Name</b>	<b>Common Side Effects</b>
<b>Opioids</b>	
Morphine	nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, respiratory depression, gastrointestinal depression and rash
Fentanyl	nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, respiratory depression, and tolerance
<b>Benzodiazepines</b>	
Midazolam	myoclonic jerking, respiratory depression, excessive sedation, and hypotension
Lorazepam	myoclonic jerking, respiratory depression, excessive sedation, and hypotension
<b>Barbiturates</b>	
Phenobarbital	sedation, depression, insomnia, and altered mood or behavior. In addition to the above side effects, there is the chance of physical dependence and severe adverse reactions with many other commonly used drugs
<b>NSAIDs</b>	

Acetaminophen	Rare side effects only, very few interactions with other medications reported.
Ibuprofen	nausea, diarrhea, headache, dizziness, fluid retention, elevated blood pressure, gastrointestinal ulceration, and bleeding
<b>Other Drugs</b>	
Ketamine	raise blood pressure and pulse rate, raise intracranial and intraocular pressure, hypersalivation, increase muscle tone, in some cases alter mood and behavior

Based on the most common side-effects, the following table (Table 2) was created to illustrate the most common side-effects of the most commonly used medications. From that information, generalizations about the impact side-effects have on growth and development are presented.

Table 2

Drug Name	Nausea/ Vomiting	Diarrhea or Constipation	Dizziness	Alteration of blood pressure	Physical Dependence	Respiratory Depression
Morphine	X	X	X		X	X
Fentanyl	X	X	X			X
Midazolam				X		X
Lorazepam				X		X
Phenobarbital					X	
Acetaminophen						
Ibuprofen	X	X	X	X		
Ketamine				X		

Some of the most common short-term side effects do not seem detrimental, as they should be short lived. However, imagine an infant, at a time that is critical for growth and development, experiencing these side-effects. An infant who should be eating, sleeping, exploring, and growing, may not feel pain, but would experience side effects that could leave lasting impressions. Many of the side effects could impact nutrition and overall growth of an infant. An infant who feels nauseous or is vomiting would most likely have little interest in food. This could impact growth and nutrition for longer than the duration of use of the medication. Additionally, if an infant is suffering from diarrhea or constipation, they would also most likely not be willing to eat.

Furthermore, when medical professionals are assessing the pain level of an infant they check vital signs. One of the most significant vital signs in assessing pain is blood pressure. Four of the most commonly used medications could either raise or lower blood pressure. This is significant when considering long-term effects of medication. If an infant's blood pressure is lowered by a side-effect of a drug then their pain may be under treated and therefore they will suffer long-term effects of exposure to pain. Pain receptors in the brain could be permanently altered, ultimately changing the way an infant responds to pain in the future. Conversely, if an infant's blood pressure is raised due to a side-effect of a drug then they may be over medicated. Again, no longitudinal studies were found regarding long-term effects of these medications. However, too much of a drug cannot be beneficial. In order to reduce drug-induced side effects and the unknown long term side effects, the amount and length of time exposed to medications should be limited (Rosen & Dower, 2011). Another potential long-term effect is physical dependence which could ultimately lead to addiction.

Addiction is a life-long affliction and could be considered a long-term effect of exposure to prescription drugs.

After researching and analyzing the effects prescription drugs have been found to have on adults, generalizations were made as to their effects on infants and their development. Table 3 offers a description of typical development and ways to support development if certain milestones are not met. As always, parents or caregivers should consult a physician if they suspect a delay of any kind.

Table 3

<b>Age</b>	<b>Developmental Milestones</b>	<b>Activities to Promote Development</b>
<b>Physical Development</b>		
One Month	Jerky motions with arms and legs	Allow infant to move freely. Encourage movement on the floor or play mat.
	Move hands towards eyes and mouth	Assist infant by moving hands towards face and away again.
	Move head side to side	Allow infant to move on back and belly. Encourage movement by moving toys from one side of their head to the other.
Three Months	Smoother Motions with arms and legs	Allow infant to move freely. Encourage movement on the floor or play mat.
	Lift head when held upright	Hold infant upright, allowing them to build strength.
	Lift head and chest when on stomach	Provide tummy time several times a day.
	Track objects or people with eyes	Encourage movement and tracking by moving toys into and out of the infant's field of vision.

Six Months	Hold head steadily	Hold infant upright, allowing them to build strength.
	Rolls over	Provide tummy time often. Encourage rolling over by placing toys on either side of the infant, just out of reach.
	Sits with assistance	Help infant to a sitting position and offer support, allowing infant to balance on their own as much as possible.
	Reaches for objects	Encourage reaching in any position by placing objects just out of reach. When infant is lying down, dangle objects over them.
	Transfers objects from hand to hand	Model and assist infant by placing objects in one of their hands and transfer to the other hand for them.
	Bangs objects together	Model and assist infant by placing an object in each hand and clap them together.
<b>Cognitive Development</b>		
One Month	Recognizes sounds and may turn in that direction	Talk, sing, read, or make noises to the infant.
Three Months	Turn toward familiar sounds	Again, talking, singing, reading, or making noise will encourage the infant to turn toward familiar sounds.
	Turn toward bright colors or light	Offer toys with bright colors and contrasting patterns.
	Respond to noise like a rattle	Play with the infant by using toys that make noise.
Six Months	Open mouth for spoon	Be consistent with feeding solid foods, this will develop familiarity.
	Imitate familiar actions of caretakers	Talk to infants as tasks are completed, label actions. Include infant in everyday actions like cleaning or cooking.

<b>Social-Emotional Development</b>		
One Month	Study faces	Spend time face-to-face with infant, this will encourage eye contact and studying of facial features.
	Prefer soft touches	Be gentle when handling infants. Provide toys and blankets that are soft to the touch.
	Respond to familiar voices and sounds	Talk, sing, read, make noises, and repeat sounds infant makes.
Three Months	Calms easily	Encourage self-soothing methods such as pacifier, finger or thumb sucking. Hold the infant and speak softly.
	Coo or gurgle	Talk, sing, make noises, and repeat any sounds infant makes.
	Cry to communicate needs	Respond promptly to infant's cries.
	Smile in response to others	Smile when interacting with an infant. Be sure to smile in response to an infant's smile.
Six Months	Babbles	Encourage infant to make sounds by responding and mimicking sounds they make.
	Recognize familiar faces	Be sure to make eye contact with infant when interacting. Name familiar people as they hold or play with the infant.
	Smile at self in mirror	Allow and encourage infant to play with toys that have mirrors. Show them their reflection and talk about who is in the mirror.
	Is able to scream, laugh, and squeal	Interacting with and responding to an infant will promote screaming, laughing, and squealing.



Table 3 is divided into three areas of development, physical, cognitive, and social-emotional. Each of the three areas is then sectioned into ages, one month, three months, and six months. There are developmental milestones listed for each age range in all three areas of development. Table 3 is meant to illustrate the timeline of a typically developing infant. The final column provides activities and ideas to further development. Infants who have been hospitalized may not meet developmental milestones when expected. The objective of Table 3 is to provide assistance in understanding typical development.

### **Effects of Physical Development**

If infants are hospitalized and essentially immobile, they are unable to develop motor skills at the typical rate. In the first month of life a typically developing infant is able to make jerky motions with arms, move hands close to eyes and mouth, and can move head from side to side when lying on stomach (American Academy of Pediatrics, 2013). At three months of life an infant who is typically developing can move with smoother motions, lift head when held upright, lift head and chest when on stomach, hold a toy that is presented, track an object or person with their eyes, and hands are no longer in fists, they are more relaxed (National Network for Child Care [NNCC], n.d.). And, by six months a typically developing infant should be doing all of the above in addition to, holding head steadily on own, reaching for objects, playing with their toes, transfer toys from hand to hand, shake and bang toys, rolling over, and sitting with minimal help (National Network for Child Care [NNCC], n.d.). All of the motor skills build on each other.

An infant who has been sedated and immobile has missed crucial time in developing motor skills. Any and all movement during infancy is assisting in the acquisition of motor

skills. Even at one month of age an infant should be moving their arms and legs, move hands towards their face, and move their head when lying on their stomach. Imagine an infant who is sedated and lying on their back, immobile. How could an infant then develop motor skills? Additionally, if an infant has not had tummy time or the opportunity to move at all they will have gross motor delays. For example, if an infant is delayed in rolling over, they may also be delayed in sitting as sitting up on their own is developed after they learn to roll over. Long-term, an infant who has gross motor delays may always have delays or difficulty with coordination. In terms of fine motor skills, infants need to manipulate objects to acquire fine motor skills. Infants who are delayed in developing fine motor skills could face difficulty with coloring, writing, zipping, or tying in the future. It seems that motor delays could be resolved with appropriate interventions.

In addition, common side effects of the most popular drugs include gastrointestinal issues, nausea, and diarrhea. How is an infant supposed to grow and have energy if they are experiencing adverse reactions to the drugs that helped them heal? According to the research, the majority of side effects are short term and reversible. However, side effects that affect the gastrointestinal system (GI system) may leave lingering side effects. Morphine has been studied more than any other drug mentioned. One of the known side effects of morphine is its effect on the gastrointestinal system. In multiple studies, morphine has shown to alter the motility of the GI system (Walter-Nicolet et al., 2010). So, if an infant's GI motility has been slowed by the effects of morphine, they are not going to eat like a typical infant would. This could affect the growth of the infant. Also, if an infant is not

eating and growing as they should, they may not have the energy or endurance needed to explore and move about their environment.

### **Effects on Cognitive Development**

How would a delay in cognitive development affect a child's long-term development? If an infant is sedated even for the first month of life, that is a significant amount of time that is lost. An infant who is sedated is not able to study faces of family members, or connect their voice to their faces. This may cause disconnect in the relationship between the infant and parents. In addition, the hospital is a bright and noisy place. Given that six month old infants should respond to both visual and auditory stimuli, could the hospital setting desensitize infants? Or, could the bright and loud hospital setting cause overstimulation? Either could lead to long-term effects, such as not responding appropriately to loud noises like sirens or alarms. Conversely, being too sensitive to sound could cause misbehavior or fear of loud noise. In terms of the brightness, potentially infants exposed to the hospital environment may not be able to sleep normally as they have grown accustomed to the brightness all day. To determine long-term effects of medication would be difficult to determine, as effects from the hospital stay and sedation itself would be difficult to extrapolate from each other.

Additionally, many drugs have the potential to create physical dependency. Addiction affects the brain in very specific ways. How would addiction alter an infant's brain development? There is little research to answer this question. The majority of research involving addiction refers to adult addiction habits or risk factors for addiction.

## **Effects on Social-Emotional Development**

With the limited interactions that sedatives and other drugs create, social- emotional development is deeply impacted. “Relationships are the way babies come to know the world and their place in it. They provide the loving context necessary to comfort, protect, encourage, and offer a buffer against stressful times” (Zero to Three: National Center for Infants, Toddlers, and Families, 2012, para. 1). Infants, who are unable to interact, would be unable to establish relationships, which is the cornerstone of social-emotional development. By one month of age, a typically developing infant is expected to recognize and respond to voices, study faces, and prefer soft touches. An infant who is sedated or in pain would either miss those experiences completely or the experience could be overridden by pain. As an infant develops, they are making connections, if they are in pain when someone touches them, they may associate pain with touch, therefore not wanting to be touched or possibly held. Also, as previously stated, if an infant is unable to study faces, they may be unable to recognize their parents, therefore potentially adversely affecting the parent-child relationship. As with other forms of development, social-emotional development builds skill upon skill. By three months of age, a typically developing infant is able to communicate through cooing, crying, or expression (Zero to Three: National Center for Infants, Toddlers, and Families, 2012). An infant, who has been sedated, may not have had the opportunity to learn to cry to elicit a response from caregivers. Also, if they do cry, they may not know what it is like to be comforted. Again, this is something that could adversely affect the parent-child relationship. Parents are supposed to be the primary caregivers, the ones who protect a child from harm. What happens when an infant is hospitalized from birth and bonding is delayed

several weeks or months? All in all, in infancy social-emotional and cognitive developments are closely related and rely on interactions, which may not happen when an infant is hospitalized.

### **Effects on Overall Health**

Upon release from the hospital, it is assumed that the patient is given a clean bill of health. However, after enduring painful procedures and multiple drugs, there may still be struggles ahead. Again, many of the drugs used as analgesics and sedatives have common side effects such as nausea, diarrhea, respiratory depression and various effects on the GI system. Many of the side effects could affect the infant's ability to eat normally. "Morphine analgesia delays the initiation and attainment of full enteral feeding" (Walter-Nicolet et al., 2010, p. 358). Although most of the side effects are said to be short term, they could alter the eating and sleeping habits of an impressionable infant. Infants should be able to suck, swallow, and breathe naturally as they eat. However, infants who have been hospitalized may not have developed that skill which is compounded by the side effects of the drugs. So, if an infant is not eating as they should, they are not consuming enough calories, which in turn mean they are not growing as they should. Therefore, nutrition is effected as well as the overall health of the infant. In addition, infants who have been hospitalized have been accustomed to a bright environment where people are around all of the time. There is no differentiation between night and day. Sleep patterns are also important for overall health and growth. There are rare instances where some drugs have been known to cause insomnia. All of these issues become intertwined when discussing development of an infant. And

again, it is difficult to know where the side-effects of the drugs and the side-effects of the hospitalization separate.

With all of the research detailing short-term effects of pain and sedation medications, one would think the same would be true for long-term effects. However, given the cost and time to conduct such studies, it appears that the medical community will continue to use these medications “off-label” for pediatric patients. This is a concern, as it is important to know both short and long-term effects. Knowing effects of medications would assist in preparation for the impact on development. And, being prepared could eliminate or significantly reduce developmental delays created by the side effects of prescription drugs. Therefore, studies should be conducted to determine long-term effects of medication.

Such studies should be conducted in the medical and educational fields. Although these studies have yet to be conducted, generalizations can be made regarding long term effects. Many of the known common short term side effects involve the gastrointestinal system, nausea, vomiting, and diarrhea. All of those side effects could impact the desire to eat. If an infant is feeling these symptoms, they may be reluctant to eat. If an infant does not eat, they do not have energy or grow. Additionally, respiratory depression is a short term side effect of several drugs. A child who is not breathing well is not able to eat well. Again, this creates poor eating habits and poor growth. Poor eating habits and slow growth could be long term effects. Long term effects on physical development could be impacted by poor growth. Physical development could also be impacted in the form of coordination, balance, and strength. Cognitive and social-emotional developments both involve communication and relationships. Long term effects from sedation could include creating and maintaining

relationships, as well as communication in general. Knowing what to expect in terms of long-term effects would allow for doctors, families, and educators to take preventative measures to ensure the success of the child. As needed as these studies are, they could be difficult to complete. Some of the long-term side effects that could be attributed to early exposure to medication could also be attributed to a diagnosis or hospitalization. Perhaps this is part of the reason for lack of research in this area.

Several trends, patterns, and gaps were found through the research literature review. Upon completing research, drugs most commonly used in NICUs were identified. The most commonly used drugs were determined to be morphine, fentanyl, midazolam, lorazepam, Phenobarbital, ketamine, acetaminophen, and ibuprofen. From the research of specific medications, similar side effects became apparent. The majority of the common side effects involve gastrointestinal issues like nausea, vomiting, and diarrhea. Other common side effects include dizziness and headache. One of the most concerning side effects that emerged is the possibility of physical dependence. The most obvious trend identified was the fact that the most common side effects are short term, no long term side effects have been identified. This trend presents a major gap in research as well.

### **Summary**

This study was conducted through extensive literature review rather than in the field due to time constraints. There was an abundance of research regarding use of medications for pain management and sedation in adult patients. However, research regarding the use of the same medications for infants is limited and longitudinal studies do not seem to exist yet. Through the use of information gathered about side-effects of the most commonly used

medications generalizations have been made about what long-term effects could be caused by early exposure to prescription medication. Finally, the growth and development of a typically developing infant is detailed and accompanied by suggestions for promoting development. Given the lack of research regarding long-term effects of prescription medication, further studies are necessary. Ultimately, the findings in this study led to more questions and the need for further study.



## **Chapter Five: Conclusion**

### **Summary of the Study**

Expectant parents are excited for the arrival of their baby. However, there are times when excitement is replaced with other emotions as hospital stays are sometimes necessary for newborns. There are a number of reasons as to why an infant could be hospitalized. During that stay an infant could be exposed to a number of medications. How does exposure to prescription drugs in infancy affect growth and development? This is the question that drove this study.

In order to attempt to discover what the long-term effects of exposure to prescription medications are documentary research was conducted. In addition to the original research question regarding long-term effects of prescription medication, several other questions arose. Other areas that were researched include narrowing the medication list to the most commonly used pain and sedation medications in Neonatal Intensive Care Units. From that list, a review of medical journal articles containing known side effects of each drug was conducted and common side effects were determined. Also the impact of side effects on physical, cognitive, and social-emotional development were considered and researched. Ultimately, the extensive literature review revealed more questions and areas for further study.

At the conclusion of this study, again more questions remained. There is no true answer to what the long-term effects of prescription medications are. Instead what was discovered was that short-term effects are known and have been researched on adults, not pediatric patients. Additionally, the Food and Drug Administration has created regulations

that are in the best interest of pediatric drug use. However, even with the regulations, doctors still have flexibility in prescribing and using drugs that are not approved for pediatric use by using them “off-label” (Luo et al., 2007). The question of long-term effects still remains. In order to generalize what the long-term effects could be, typical development was discussed along with delays or complications in development. The most significant finding is that the medical community has studied short term side effects of these medications, but long term side effects have not been studied. Therefore, the greatest conclusion that can be made is that there is a need for further study.

### **Conclusion**

Although the research did not conclusively answer the question of long-term effects of prescription medication, there are many conclusions that can be made. One of the most significant conclusions that can be drawn from the research is that perhaps the medical community does not see a need for further study in this area. In terms of surgery or a medical diagnosis, medical staff is only concerned with saving a life. Once a patient has been discharged from the NICU, they may not see the surgeons, doctors, and nurses that are responsible for saving their life. Therefore, those same surgeons, doctors, and nurses are not the medical staff who would have the opportunity to observe long-term effects of medications. Along the same lines, the medical community is known to use drugs “off-label” and can see their immediate effects. So, why be concerned about long-term effects when the infant is surviving?

The Food and Drug Administration has created regulations in an attempt to protect pediatric patients. However, those same regulations make it possible for medical

professionals to use drugs “off-label” as they see fit. And, the process to label drugs for pediatric use is extensive and costly. So, why study long-term effects when drugs can be used “off-label” and help save lives?

Armed with the knowledge of adverse effects of both exposures to pain versus the side effects of analgesics, the research indicates that medication wins. Given that exposure to pain could alter neurological pathways, the side effects of some drugs seem to make less of a permanent impact but a great short term solution. There is clear evidence that early exposure to pain can be more detrimental to the development of an infant than some of the side effects of the medications. If an infant is exposed to pain, especially during critical developmental times, then the pathways in the brain that recognize pain could be altered permanently. With that said, it then becomes even more obvious that there is a need for longitudinal studies on the long-term effects of prescription medication.

As a child grows and develops, they are expected to meet certain milestones along the way. Children who have been exposed to medications during infancy could suffer long term effects. During a hospital stay, an infant who is sedated is not moving, and therefore not developing. As discussed previously, there are critical times for development. How does early exposure to prescription medications effect development? As discussed previously, there are critical times for development. Could lack of movement in infancy lead to poor muscle tone and lack of strength later on? Could lack of movement in infancy lead to poor muscle tone and lack of strength later on? Even with interventions some children may not develop and develop a delay places them further and further behind their typically developing peers. Also, if a child is not developing at a typical rate and lacks strength, they

may also lack appropriate balance and coordination. In regards to fine motor development, without the opportunity to open their hands and manipulate objects could have fine motor difficulties which impact writing, coloring, drawing, and dressing themselves. Also, without the movement of their hands, a child may not develop effective hand-eye coordination. Additionally, due to delays in growth from a hospital stay and potential side effects from medication, a child who has been exposed to analgesics and sedatives may be shorter and thinner than their peers. This could be due to side effects that medications have on the GI system or the fact that eating habits could be impacted as well. All in all, the physical development of children who have been exposed to prescription drugs during infancy could be impacted for many years.

How would a delay in cognitive development affect a child's long-term development? An infant who is sedated is not able to study faces of family members, or connect their voice to their faces. This may cause disconnect in the relationship between the infant and parents. Can this potential disconnect or lack of bonding be reversed? How would this impact the development of a parent-child relationship? Also, how would this disconnect affect the development of other relationships? In addition, the hospital is a bright and noisy place. Given that six month old infants should respond to both visual and auditory stimuli, could the hospital setting desensitize infants? Or, could the bright and loud hospital setting cause over stimulation? Either could lead to long-term effects, such as not responding appropriately to loud noises like sirens or alarms. Conversely, being too sensitive to sound could cause

misbehavior or fear of loud noise. In terms of the brightness, potentially infants exposed to the hospital environment may not be able to sleep normally as they have grown accustomed to the brightness all day.

Social-emotional development can be greatly impacted by the use of analgesics and sedatives. Infants who are medicated would be unable to interact and therefore unable to establish relationships, which is the base of social-emotional development. Typically developing infants are expected to recognize and respond to voices, study faces, and prefer soft touches by one month of age. An infant who is sedated or in pain would either miss those experiences completely or the experience could be overridden by pain. As an infant develops, they are making connections, if they are in pain when someone touches them, they may associate pain with touch, therefore not wanting to be touched or possibly held. Also, as previously stated, if an infant is unable to study faces, they may be unable to recognize their parents, therefore potentially adversely affecting the parent-child relationship. As with other forms of development, social-emotional development builds skill upon skill. By three months of age, an infant should be communicating through cooing, crying, or expression (Zero to Three: National Center for Infants, Toddlers, and Families, 2012). An infant, who has been sedated, may not have had the opportunity to learn to cry to elicit a response from caregivers. Also, if they do cry, they may not know what it is like to be comforted. Again, this is something that could adversely affect the parent-child relationship. Parents are supposed to be the primary caregivers, the ones who protect a child from harm. What happens when an infant is hospitalized from birth and bonding is delayed several weeks or months?

## **Suggestions for Promoting Development**

Development of an infant can be broken into the three categories of physical, cognitive, and social-emotional development. However, in terms of fostering development, many of the activities overlap and intertwine. The basic premise for infant development is to interact and play with them. As previously stated, cognitive and social-emotional development hinge on interaction. This is difficult to do when an infant is discomforted or sedated. However, most infants have fully developed hearing, so talking, humming, or singing can be a great way to connect with an infant who is sedated. Additionally, touch is important. Parents can still touch their infant as they are talking to them to help facilitate a relationship. It is not always possible to hold an infant who is hospitalized, but that would be best if possible. Simply holding an infant helps develop motor, cognitive, and social-emotional skills all at the same time. While in the hospital, there is typically a support system known as the Child Life Specialists. They are in place to assist in keeping infants comfortable, promotion of development, and fostering parent-child relationships. Child Life Specialists are a great resource while an infant is in the hospital (Regents of the University of Michigan, 2013).

How can parents support development after discharge? Again, interacting and playing with an infant is the best way to promote development. Also, talking to an infant using various tones and making eye contact will stimulate social-emotional and cognitive development. Reading, singing, and telling stories will also foster cognitive and social-emotional growth. As an infant grows, they begin to coo and make sounds. Repeating the sounds or words an infant makes will also assist in their development. Promoting motor

development involves encouraging an infant to explore and manipulate objects. Parents can model and encourage touching, banging, stacking, and shaking of toys. Also, tummy time is extremely important in the development of motor skills. Spending time on the floor with an infant will help them develop motor skills.

There are resources for parents who have concerns about the growth and development of their child. All states have early childhood programs of one sort or another. Infants with developmental delays could receive occupational therapy, physical therapy, and speech therapy based on their needs. Additionally, maintaining contact with an infant's pediatrician or family doctor is crucial in assuring that a child with a delay is receiving all they need to grow and develop.

### **Recommendations**

Given the lack of longitudinal studies on the long-term effects of medications on the growth and development of an infant, the first recommendation would be to conduct longitudinal studies. There are many known short-term side effects of medications that could alter development and behaviors. Additionally, the long-term effects of early exposure to pain are known and well documented. The same should be true for long-term effects of medications. There is a significant need for longitudinal studies that not only determine long-term effects on health, but also overall development. From these studies, programs could be developed to assist families foster the growth and development of their child.

The need for longitudinal studies is apparent. Such studies should be conducted in both the medical and educational fields. From a medical standpoint, studies need to be conducted to determine effects on growth and development. Any side effects that could be

avoided or corrected as soon as possible would be the ultimate goal of medical studies. Educational studies, on the other hand, would target how developmental delays and/or medical issues affect a child's ability to learn and function in a classroom environment. In order for these types of studies to become a reality, the medical and educational communities would need to collaborate.

In order for longitudinal studies to be conducted the Food and Drug Administration will need to be involved. Although there are some regulations regarding labeling medications for pediatric use, there are areas for improvement. Currently, drugs approved for pediatric use must go through a rigorous approval process which includes conducting studies on pediatric participants. However, there are ways around the extensive, costly process. Companies can get their drug approved for "off-label" use and therefore, they do not have to comply with FDA regulations if there is a need for a medication. An example of such medication would be morphine. Morphine has been studied extensively on adult patients and a need has been shown for use in pediatric patients. Given that information, the FDA should alter their regulations and make it mandatory that all medications given to pediatric patients have a pediatric label.

Ultimately, this study has shown that there is a gap in the research regarding long-term effects of early exposure to prescription medications. Given that there is such a gap in knowledge, there is a need for further study. Longitudinal studies should be conducted in the medical and educational fields to truly assess the long-term effects of medications. For now, known short-term side effects can be used to hypothesize potential long-term side effects.



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**695 DATA FORM**

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<input type="checkbox"/> Adult & Higher Ed	<input type="checkbox"/> Ed Differentiation	<input type="checkbox"/> Library Media
<input type="checkbox"/> Advanced Content Spec	<input type="checkbox"/> Ed Leadership	<input type="checkbox"/> Middle Level Ed
<input type="checkbox"/> Cognitive Impairment	<input type="checkbox"/> Ed Technology	<input type="checkbox"/> Reading
<input type="checkbox"/> CSAL	<input type="checkbox"/> Elementary Ed	<input type="checkbox"/> School Counseling
<input checked="" type="checkbox"/> Early Childhood	<input type="checkbox"/> Emotional Impairment	<input type="checkbox"/> Secondary Level Ed
<input type="checkbox"/> ECDD	<input type="checkbox"/> Learning Disabilities	<input type="checkbox"/> Special Ed Admin
<input type="checkbox"/> TESOL		

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| 1. Effects of prescription medication | 6.  |
| 2. Commonly used medication in NICU   | 7.  |
| 3. Early exposure to medication       | 8.  |
| 4. Early exposure to pain             | 9.  |
| 5. Pain management for infants        | 10. |