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Pharmacological Pain Management in Pediatric Sickle Cell Pain Crisis: An Integrative Review

Brenda Middlebrooks
bmiddlebrooks2@liberty.edu

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Pharmacological Pain Management in Pediatric Sickle Cell Pain Crisis: An Integrative Review

Brenda Middlebrooks

Liberty University

ABSTRACT

Pain management among pediatric patients with sickle cell disease continues to pose a challenge to healthcare providers. Underlying disease processes, family perceptions of painful events, and injury add to the complexity of effective pain management in this population. Sickle cell disease is the most common variant of the many hemoglobinopathies in the world, with painful episodes as the most common presentation to emergency departments for treatment beginning as early as 6 to 8 months of age. Sickle cell pain crisis continues to receive less-than-effective pain management treatment resulting in frequent hospitalizations, chronic pain, and increased morbidity and mortality. This integrative review provides a synthesis of the published evidence regarding the best approach to pharmacological management of pain during sickle cell pain crisis in the pediatric population. Results of these studies strongly correlate pharmacological pain management of pediatric sickle cell crisis pain on consensus and expert opinion with few strong research studies conducted to completion. The literature also suggest new knowledge in the areas of pathophysiology and pharmacogenomics in provider decisions in pharmacological management of pediatric sickle cell crisis pain is not seen in clinical practice resulting in undertreatment and repeated hospital admissions. The undertreatment of pediatric sickle cell crisis pain contributes to morbidity and early mortality in this patient population.

Keywords: pediatrics, sickle cell pain crisis, pain management, pharmacogenomics

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PAIN MANAGEMENT IN PEDIATRIC SICKLE CELL CRISIS PAIN

Sickle cell disease is an autosomal recessive inherited hemoglobinopathy, which occurs in one in every 500 African American births (Raphael, Tran, Mueller, & Giardino, 2013). The hallmarks of this disorder are sickling of erythrocytes, occlusion of small blood vessels, and pain. These vaso-occlusive painful crises are debilitating and are medical emergencies (Morris et al., 2013). Although 78% of 200,000 emergency room visits annually for patients with sickle cell disease are for pain, 60% of those visits are among the pediatric population. Children with sickle cell disease utilize healthcare services at a rate 8.8 times that of children in general, and have increased hospitalizations and longer hospital stays than children with other chronic illnesses, with an estimated average healthcare cost of approximately \$1,354,000 during childhood (ages 0-21) (Raphael et al., 2013).

Many advances in the treatment of sickle cell disease have extended the life expectancy from early childhood/young adulthood in the period 1950-1980, to a more recent range of 50 to 70 years in high-income countries such as the United States (Ballas, 2014). Sickle cell disease is multifaceted, including neurological compromise, acute chest syndrome, sickle cell crisis pain, and organ damage. Sickle cell crisis pain accounts for approximately 70% of all emergency department visits for children with sickle cell disease (Fein, Avner, Scharbach, Manwani, & Khine, 2017). Treatment of pediatric sickle cell pain crisis remains an area experiencing minimal improvement toward effective management. Healthcare providers are beginning to research areas of pain management utilizing a multimodal model to address the effective relief, intensity, and frequency of pain symptoms among the pediatric population.

This integrative review will provide a discussion of published literature related to evidence-based pharmacological pain management strategies in the hospital setting for the pediatric sickle cell patient experiencing a pain crisis. This review will contribute to the practice of pain management of the pediatric sickle cell patient in pain crisis for the advance practice nurse with improvement in the relief, intensity, and frequency of pediatric sickle cell pain crisis. The focus of this integrative review is to analyze and synthesize the literature to present evidence-based approaches to pharmacological management of pain during sickle cell pain crisis in the hospitalized pediatric population.

Background

Pain and Pediatric Sickle Cell Disease

Understanding the mechanisms of pain in the sickle cell patient directs the effective treatment and research into new treatment regimens in the relief of pain, decrease in pain intensity, and pain frequency resulting in hospitalizations. Sickle cell pain crisis is defined by the different types of pain and area of the nervous system impacted. Intermittent vaso-occlusive pain crisis, defined by the lack of pain between episodes, is most common among the pediatric sickle cell population. Because the dorsal horn is the main pathway to the central nervous system, inhibiting and minimizing the transmission of painful stimuli begin here with pain relief efforts by endogenous endorphins (Ballas, 2014). The second step is to control the transmission of painful stimuli through the two sodium channel receptors, which determine the type, severity, and duration of the vaso-occlusive pain crisis. These sodium channels, α -Amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) channels, allow for effective relief of pain with non-opioids and opioids unless aberrant metabolism of opioids exists for intermittent vaso-occlusive pain crisis (Ballas, 2014).

Pain and Pharmacogenomics in Sickle Cell Disease

Pharmacogenomics has become a new field of research for improvement in pain management among pediatric sickle cell pain crises. Understanding of the metabolic pathway will assist healthcare practitioners in the development of individualized pain management treatment plans to correct the undertreatment of pediatric sickle cell pain crisis. Traditionally nonsteroidal anti-inflammatory drugs (NSAID) and opioids are the backbone of pain management in children with sickle cell disease (Jaja, Patel, Scott, Gibson, & Kutlar, 2014; Yee et al., 2013). Many African Americans and those of African descent are affected by genetic variations in the CYP2D6 gene, which may contribute to poor metabolizing of opioid medications requiring this pathway in obtaining pain relief (Yee et al., 2013). According to Jaja et al. (2014), African American children with sickle cell disease have a slightly higher frequency of the CYP2D6 gene deletions compared to healthy African Americans. Many pediatric patients experience adverse reactions of narcotic administration, such as respiratory depression and euphoria, without any analgesic effect (Yee et al., 2013). Notably, the CYP2C9 allelic variant study showed 30% of children with at least one allele associated with reduced function in metabolizing NSAIDS resulted in decreased analgesic effect and increased toxicity (Jaja et al., 2014). Impaired NSAID metabolism is strongly associated with the following adverse effects among children with sickle cell disease treated for sickle cell crisis pain: gastrointestinal complications, renal impairment, fluid retention, and exacerbation of asthma (Jaja et al., 2014). Understanding the metabolic pathway of the most commonly used medications in the treatment of pediatric sickle cell crisis pain could potentially enable clinicians to identify patients with impaired CYP2C9 metabolic capacity, enabling clinicians to make distinctions between a

compliance problem and a metabolic defect, and tailor NSAID dosing accordingly to achieve optimal analgesic response (Jaja et al., 2014).

At this time feasibility of genetic testing is not available; therefore, clinicians must use clinical signs and symptoms of failed opioid and NSAID treatment of sickle cell pain crisis and seek other adjuvants to obtain pain relief and decrease in pain intensity and pain frequency.

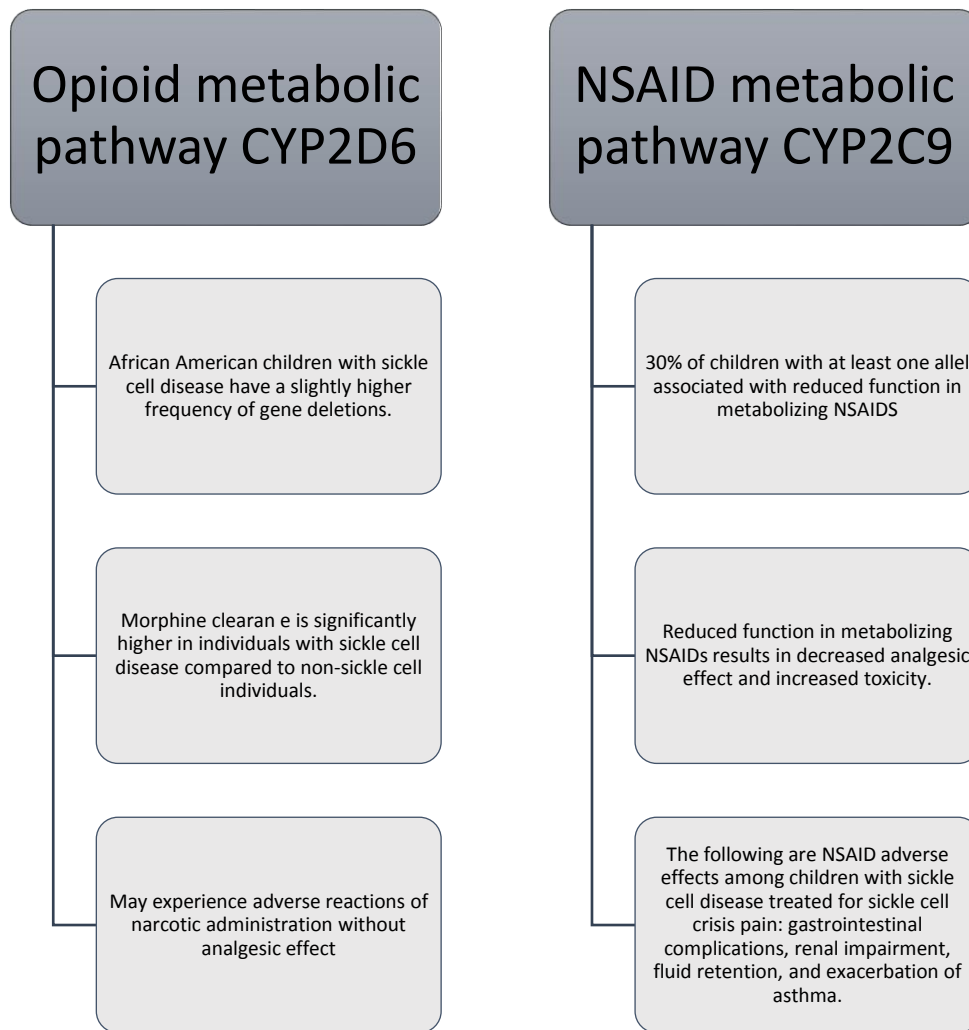


Figure 1. Effects of gene deletions and allelic variants in the opioid and NSAID metabolic pathways. Adapted from Yee et al., 2013; Jaja et al., 2014.

Pharmacological Pain Management and Sickle Cell Pain Guidelines

Many of the recommendations are based on weak evidence or recommendations related to expert opinion, consensus, and studies from pain in children with cancer (National Heart, Lung, and Blood Institute, 2014; World Health Organization, 2012). The World Health Organization (WHO) guidelines use a 2-step approach to address pain in children with medical illnesses based on strong recommendation with low quality of evidence (World Health Organization, 2012). According to WHO, the first step is the treatment of mild pain with paracetamol and ibuprofen. The second step is the treatment of moderate to severe pain utilizing opioids, with morphine as the drug of choice. The WHO guidelines of 2012 do not recommend the use of steroids in the treatment of pediatric sickle cell crisis pain or tramadol, due to a lack of available evidence of effectiveness and safe use in children (World Health Organization, 2012). These guidelines are not specific to sickle cell crisis pain but address this patient population in the discussion. According to Sheely (2015), treatment of sickle cell crisis pain has poor levels of evidence based on observational studies and expert opinion rather than clinical trials (Sheehy, Finkle, Darbari, Guerrero, & Quezado, 2015). A multicenter research study has been undertaken with a focus on the mechanism of sickle cell crisis pain with intravenous magnesium, as have a few studies with oral magnesium to address the pathophysiology of sickle cell crisis pain in the prevention of pain instead of treating sickle cell crisis pain in children (Badaki-Makun et al., 2014).

Pharmacological Pain Management and Sickle Cell Pain Research Trials

The majority of pain research has been among cancer patients and adults. Gaps exist in the literature on pain research specific to pediatric sickle cell patients. Effective management of sickle cell crisis pain in children in the emergency department and hospital setting utilizes three major classes of medications: opioids, non-opioids, and adjuvants (Hagedorn & Monico, 2016).

Much of the research has focused on narcotic sparing interventions such as arginine, which is a substrate of nitrous oxide production. Arginine is considered safe, inexpensive, and narcotic sparing, which is important in the treatment of children with concerns for opioid metabolism as an adjuvant in the treatment of pediatric pain crisis (Morris et al., 2013). Pain management treatment for sickle cell patients who have failed typical pain management with opioids utilizes ketamine, intranasal fentanyl, dexmedetomidine, gabapentin, and methadone for its analgesic effect among the pediatric population. Ketamine infusion is viewed as an effective adjuvant in the hospital setting in treating pediatric sickle cell pain and the safe monitoring and treatment of any adverse reactions to this medication (Hagedorn & Monico, 2016).

Problem Statement

Noted as an accepted world health concern with associated morbidity and mortality, the treatment of pediatric sickle cell pain crisis needs to be addressed among healthcare practitioners. Improving quality of life, enhancing life expectancy, obtaining pain relief, and decreasing pain intensity and frequency resulting in fewer emergency department visits and decreased length of stay all outline the multimodal dynamics of pediatric sickle cell pain crisis. Pediatric sickle cell pain crisis pain management continues to be undertreated and difficult to treat. According to Ender et al. (2014), patients who reported high pain scores in sickle cell crisis pain historically have increased risk of early death compared to patients who reported the lowest pain scores. Improvement in the management of sickle cell crisis pain may help prevent hospitalizations, morbidity, and mortality associated with sickle cell disease pain (Cacciotti, Vaiselbuh, & Romanos-Sirakis, 2017; Lin, Strouse, Whiteman, Anders, & Stewart, 2016).

Purpose and Significance of the Scholarly Project

The purpose of this scholarly project is to present evidenced-based pharmacological pain management strategies in the care of sickle cell pain crisis within the pediatric population. The management of pediatric sickle cell involves an understanding of its pathophysiology and available treatment methodology available to healthcare providers. These strategies will advance the practice of nursing in providing supportive care and symptom management, and improving quality of life and life expectancy for children diagnosed with one of the world's largest hemoglobinopathies.

Sickle cell disease is the most common genetic hematological disorder in the United States (U.S.). One in every 375 African-Americans is affected by sickle cell disease, with U.S. estimates of 72,000 to 98,000 when corrected for early mortality (Lin et al., 2016). The leading causes of mortality among people with the diagnosis of sickle cell disease include bacterial infections from encapsulated organisms (38.4%), cerebral vascular accident (12.3%) with acute pain crisis, and acute chest syndrome at 11%, with sickle cell pain crisis as the most common presenting complication of this disease (Lin et al., 2016). Sickle cell pain crisis is associated with increased risk of acute chest syndrome and mortality; thus, improvement in pain management among children with sickle cell disease could help decrease acute chest syndrome and mortality from sickle cell disease. The need exists for healthcare providers to do the following:

1. Understand the mechanism of sickle cell crisis pain, and the impact of undertreatment of pediatric sickle cell pain crisis.
2. Provide evidence-based and expert opinion in the development of pain management strategies and guidelines.

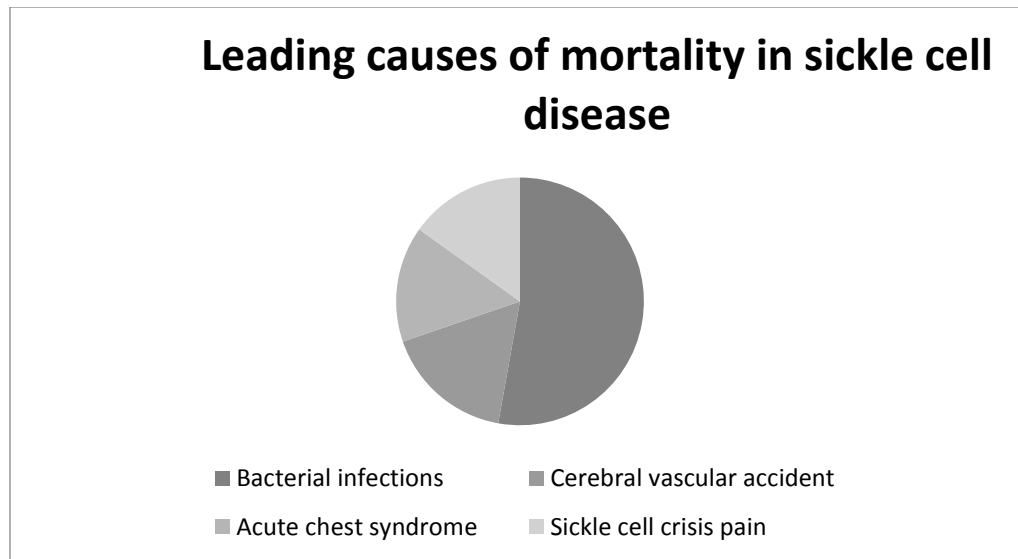


Figure 2. Leading causes of mortality in sickle cell disease (Lin et al., 2016).

Clinical Questions

This integrative review will address the following clinical question: What is the best pharmacological approach in the management of sickle cell pain crisis in the hospitalized pediatric patient?

Questions to support and maintain focus of this review:

1. What evidence-based pain management strategies have been found to be safe and effective in the management of sickle cell pain crisis in the hospitalized pediatric patient?
2. What best practices in pharmacological management support safe and effective treatment of pediatric sickle cell crisis pain?

The goals of this project will be:

1. To provide a systematic integrative review of the literature related to pharmacological pain management of pediatric sickle cell pain crisis.
2. To provide recommendations for the treatment of pain in the hospitalized pediatric sickle cell pain crisis patient.

Methods

Scientific reviews influence the definition of knowledge and clinical practice within the healthcare environment. The conceptual framework developed by Harris Cooper (1982) was the methodology used for this integrative review providing the rigor and validity needed in the synthesis of evidence related to pharmacological pain management of pediatric sickle cell pain crisis. This framework enables the project leader to provide evidence-based research findings, guidelines, and reviews to healthcare practitioners in a concise report that highlights any bias, limitations, need of further research, and practice implications (Cooper, 1982). An integrative review is performed to explore the use of pharmacological treatment of sickle cell crisis pain among children with sickle cell disease. The Liberty University Institutional Review Board (IRB) application number 3189 was approved (see appendix D for approval letter). The focus of this integrative review is to summarize past guidelines, reviews, and research of pharmacological treatment of children with sickle cell crisis pain, presenting a current state of knowledge.

Framework

The framework for this scholarly project is rooted in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions (Liberati et al., 2009). The foundational framework for the scholarly project is defined by Harris Cooper (1982). In addition, the tool used for analyzing the literature is from the guidelines of Melnyk and Fineout-Overholt (2011) for critiquing evidence.

PRISMA Statement

The purpose of the PRISMA system is to provide essential tools needed for summarizing evidence accurately and reliably to assess the risk and benefits of a healthcare intervention. The

PRISMA statement embraces a 27-item checklist and a four-phase flow diagram consisting of identification, screening, eligibility, and inclusion of retrieved literature to provide consistency in the process and documentation of reviews across all healthcare disciplines (see Appendix A for PRISMA flow diagram). The essential items for reporting were based on the 27-item checklist to ensure transparent reporting of systematic reviews, reducing the risk of flawed reporting of systematic reviews.

Melnyk and Fineout-Overholt Critiquing Evidence

The tool used for analyzing the literature is from Melnyk and Fineout-Overholt's (2011) guidelines for critiquing evidence (Appendix C). The concept presented has a focus on viewing the research for the contribution it can make to practice, instead of looking for study flaws in determining inclusion as evidence during the appraisal process (Fineout-Overholt, Melnyk, & Schultz, 2005). According to Fineout-Overholt, Melnyk, and Schultz (2005),

The purpose of critical appraisal is to determine the value of the research to practice by answering the following questions: (1) Are the results of the study or systematic review valid? (2) What are the results? (3) Are the findings clinically relevant to my practice? (p. 339)

The guideline discusses seven levels of evidence, with level 1 as the most rigorous, including systematic reviews, randomized controlled trials, and guidelines based on systematic reviews or meta-analysis, to level 7 for expert opinion. Case studies, cohorts, and qualitative studies are described in the level of evidence table. An algorithm is used to guide the literature-critiquing process, utilizing a step-wise flow to determine the level of evidence.

Cooper

This scholarly activity is a rigorous process used to synthesize separate evidence-based findings into a coherent whole (Cooper, 1982), providing a summary of the accumulated scientific knowledge concerning the pharmacological treatment of sickle cell crisis pain, bringing to the forefront research that was left unresolved. There are five phases to the integrative review process: problem formation, data collection, evaluation of data points, data analysis and interpretation, and presentation of results (Cooper, 1982). Each phase of the process addresses threats to validity and ways to protect from threats to validity, enabling the project leader to make fine distinctions between research study and review-based inferences providing optimal criteria as practice guidelines. This process outlined by project leaders was closely followed to decrease bias and inaccuracy, and to maintain academic rigor.

Problem Formulation Stage

This stage defines parameters and focus for the review process, clearly identifying the problem and defining variables of interest. The problem addressed in this integrative review of the literature is the best pharmacological approach in the management of pain during sickle cell pain crisis in the pediatric population. Points of interest for the project include currently available guidelines for pediatric sickle cell pain crisis, relevant pharmacological research in treatment of pediatric sickle cell pain crisis, and factors contributing to the paucity of completed research among children with sickle cell pain crisis. Other considerations of interest include factors contributing to adherence or non-adherence to guidelines or protocols. According to Ballas (2014), although there are many advances in the treatment of sickle cell disease, minimal advances are noted in the management of pediatric sickle cell pain crisis. The World Health Organization (WHO, 2012) and the National Heart, Lung, Blood Institute (NHLBI, 2014) reports identified early initiation of analgesics in the relief of pain symptoms. Many of the guidelines are

based on consensus and expert opinion due to the limiting factor of incomplete research trials related to patients presenting in distress, hindering their ability to give consent/assent, according to Nottage et al. (2016).

Data Collection Phase

The data collection stage of the review process involves identifying the population of interest and relevant elements of inquiry (Cooper, 1982). The project leader has recognized that one threat to validity is associated with retrieved studies not including all studies pertinent to the topic of interest, the pharmacological pain management of sickle cell pain crisis in children. Nevertheless, the project leader has utilized the online information retrieval technique, using key words and phrases to obtain the maximum number of eligible studies.

Information Sources

Bibliographic databases, ancestry approach, and the *Science of Social Science Citation Indexes* strategies were employed. The bibliographic search was performed using a comprehensive, computer-assisted online search of EBSCO host, the *Cumulative Index of Nursing and Allied Health Literature* (CINAHL), ProQuest, and Medline databases. The search included dates from January 2012 to December 2017. The ancestry and *Science of Social Science Citation Indexes* strategies were used to identify key studies within the search criteria dates. Key terms used for the search include *pediatric*, *sickle cell pain crisis*, and *pain management*. Boolean operators were used to refine and help focus the search (Holly, Salmond, & Saimbert, 2017). To determine the adequacy of the literature search strategies and to refine skills of the project leader, a professional librarian was consulted.

Eligibility Criteria

Defining eligibility criteria of the patient population, inclusion, and exclusion criteria guided the data collection phase of this review. The pediatric patient population is defined as 0 years to 21 years, which will allow for generalizations among pediatric patients with sickle cell pain crisis. The search of the literature included publications from January 1, 2012 to December 11, 2017, to obtain the most recent research and assess for areas of further inquiry. Criteria for using publications included pharmacological intervention subject matter, full-text availability, English-language reports, and U.S.-based research trials. Eligibility criteria for data collection was supported by inclusion and exclusion criteria found in Table 2.

Literature Search Results

Utilizing EBSCO host, the *Cumulative Index of Nursing and Allied Health Literature* (CINAHL), ProQuest, and Medline databases with inclusion dates from January 2012 to December 2017, the search results identified 1,565 studies, guidelines, and reviews with no other studies from other sources identified using the following key words: pediatrics, sickle cell pain crisis, pain management. Of the 1,565 articles, 489 were duplicates. During the screening process, the researcher reviewed summaries for the 1,076 studies, guidelines, and reviews remaining after duplicates were extracted. Further review excluded 1,020 studies not meeting established inclusion criteria, leaving 56 full-text studies to assess for eligibility. Continued assessment resulted in the exclusion of 35 additional studies based on pre-set inclusion criteria, leaving 21 studies, reviews, and guidelines for critical review. The critique and analysis of the 21 publications will be available in Tables 2-5.

Data Evaluation Stage

During the data evaluation stage, data in the literature meeting criteria will undergo critical judgment by the reviewer (Cooper, 1982). Primary and secondary sources were examined and a determination made to evaluate if multifactorial contamination irrelevant to the problem of interest had occurred (Cooper, 1982). Evaluation criteria were developed by the reviewer prior to beginning the literature search, and only one reviewer was utilized during this process.

Data Analysis Stage

This stage of the integrative review process incorporated the synthesizing of the evidence into a coherent statement about the research question (Cooper, 1982). A matrix in a table format was used to organize, categorize, and summarize data according to the project clinical focus (see Tables 2-5). The Nursing: Melnyk Pyramid (2011) I-VII leveling system was utilized in the evaluation and analysis of the data sources (see Appendix C for Melnyk Pyramid). The sources' theoretical information (pharmacological management of pediatric sickle cell crisis pain); evaluation information including level of evidence and source; and methodological data (sample size and setting) support for specific clinical questions were documented across studies consistently. Records were kept during the data analysis process to ensure analytical integrity.

Data reduction. The reduction phase, which identified data according to subgroups to promote effective management and maintain methodological rigor with the clinical question guiding the focus, was performed in two sub-phases. First, subgroups classifications based on level of evidenced were analyzed. The second sub-phase of reduction involved organization of the extracted data into a manageable framework for display.

Data display. The extracted data were displayed within three matrices. Each matrix represented an enhanced visualization of patterns across all data sources. In a visual format, each matrix provides an organized record of relevant results for the literature (Holly et al., 2017).

Data comparison. During the data comparison step of the integrative review patterns, themes and relationships in the literature were identified. Diagrams displaying this visual concept of the extracted data provided a visual systematic critical analysis and meaning of the review findings. This visual diagram made the depiction of relationships, patterns, and themes easier to capture.

Conclusion drawing and verification. According to Holly et al. (2017), findings from the literature serve as data and appear as themes, metaphors, and key concepts that are developed into succinct summaries of the findings. As commonalities and differences become apparent and identified generalizations are formed, constructing a new comprehensive depiction of the subject matter integrating all subgroups occurs during this process. Cooper (1982) stated the value of a quantitative integrative review as follows: “The question is still open, and both sides will probably revise their position before the debate is over” (p. 298).

Presentation of Results

Cooper (1982) described the translation of notes, printouts, and remembrances into a public document as the presentation of the inquirer’s efforts to disseminate accumulated knowledge to the scientific community. Data from the literature sources meeting inclusion criteria were displayed and organized for ease of reader access to data points. To accomplish this task, the DNP graduate employed the use of concept diagrams, tables, and flowcharts accompanied by a narrative of the results. Tables were organized including level of evidence, source, focus of literature source, conclusions, implication for practice, and recommendations. Concept diagrams were used to illustrate the major themes, patterns, relationships, and recommendations identified.

Evaluation Methods

Results

There were 21 quantitative research articles included in the integrative review (see Table 1). The types of design included the following: two level-1 systematic reviews of randomized control trials (Badaki-Makun et al., 2014; Brandow et al., 2016); seven level-2 randomized control trials (Brousseau et al., 2015; Fein et al., 2017; Horst, Frei-Jones, Deych, & Shannon, 2016; Morris et al., 2013; Nottage et al., 2016; Jaja et al., 2014; Yee et al., 2013); one level-3 controlled trial with no randomization (Ender et al., 2014); three level-5 systematic reviews of descriptive studies (Ballas, 2014; Hagedorn & Monico, 2016; Neri, Pestieau, & Darbari, 2013); six level-6 descriptive observational designs (Cacciotti et al., 2017; Krishnamurti et al., 2014; Lin et al., 2016; Raphael et al., 2013; Sheehy et al., 2015; Sheehy et al., 2017) and two level-7 expert opinions (National Heart, Lung, and Blood Institute, 2014; World Health Organization, 2012). Results of the integrative review receive further discussion using descriptive narratives and diagrams of significant concepts.

Pain and Pediatric Sickle Cell Disease

What should healthcare providers understand about the mechanism of sickle cell crisis pain?

Four of the 21 studies discussed the mechanism, pathophysiology, and pharmacogenomics of sickle cell crisis pain (Ballas, 2014; Jaja et al., 2014; Raphael et al., 2013; Yee et al., 2013). These articles focus on two major pain pathways in the treatment of sickle cell crisis pain. The first pathway allows travel of the pain stimuli to the central nervous system while sodium channel receptors determine the type, intensity, and duration of sickle cell crisis pain. Healthcare providers treating sickle cell crisis pain should administer parental opioid with frequent reassessment of pain relief. Upon further evaluation of pain symptoms, combination therapy of NSAIDs and adjuvants may be necessary, understanding the presence of hyperalgesia and allodynia are symptoms of neuropathic pain. Informed clinicians are equipped to recognize medication failure as a genetic variant and metabolic deficiency of ineffective pain management and to administer effective medication and dosage in treating children with sickle cell crisis pain.

When considering pharmacological treatment of sickle cell crisis pain, opioids and NSAIDs remain the backbone of treating pediatric sickle cell crisis pain in the hospital setting. The field of pharmacogenomics assists the healthcare provider in identifying patients with genetic variations of the CYP2D6 and CYP2C9 pathways contributing to poor pain response and repeated failed emergency department management of pediatric sickle cell crisis pain. Among African Americans, genetic variants of the CYP2D6 pathway for opioid metabolism are higher among those with sickle cell disease. Healthcare providers should be aware that 30% of children with sickle cell disease may also have a CYP2C9 genetic variant decreasing the analgesic effect of NSAIDs, with an increase in adverse reactions. Understanding of the pathophysiologic

mechanism and pharmacogenomics of management of children experiencing sickle cell crisis pain has improved, although clinical management of sickle crisis pain does not reflect new knowledge.

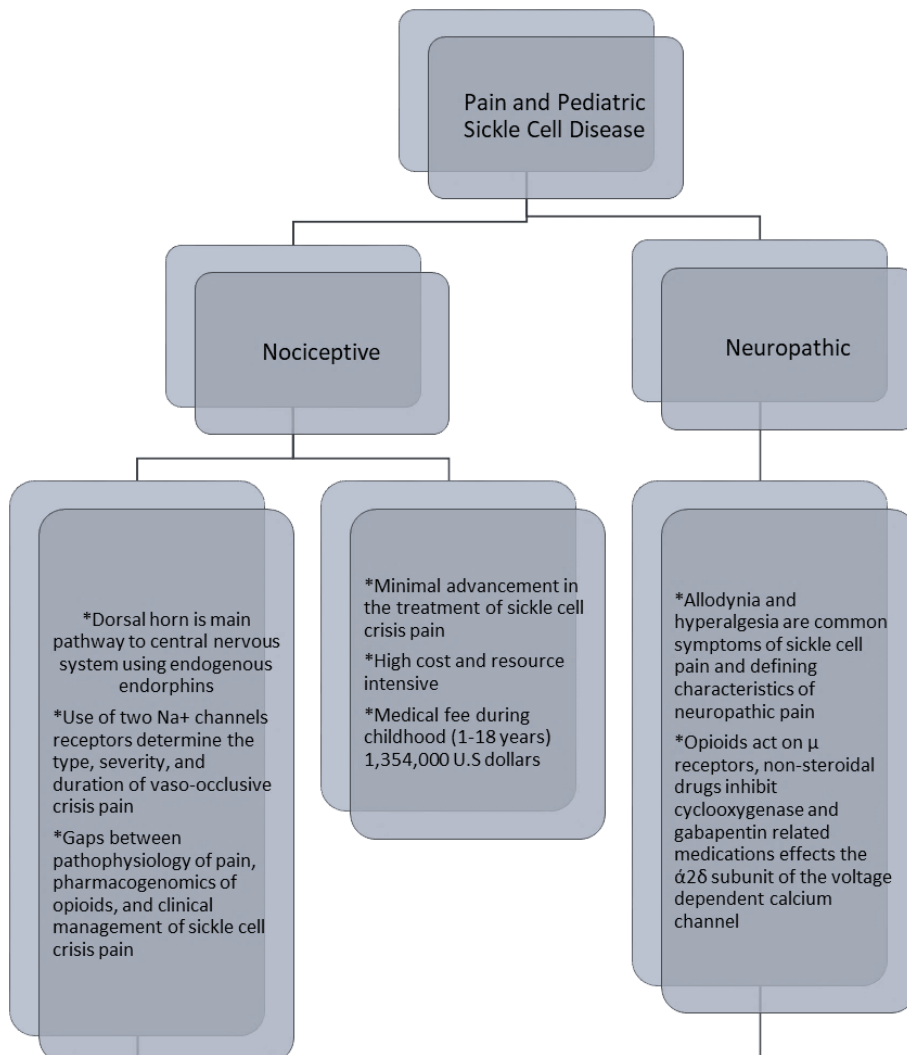


Figure 3. Flowchart of pain and pediatric sickle disease theme. Adapted from Ballas, 2014; Nottage et al. 2016; Raphael, Tran, Mueller, and Giardino, 2013; Yee et al., 2013.

Pain Management and Pediatric Sickle Cell Pain Guidelines

What are the currently available guidelines in the treatment of pediatric sickle cell pain crisis and barriers to healthcare providers?

Four of the 21 studies discussed guidelines for the treatment of pain management of pain in children with medical illnesses, sickle cell crisis pain, definitive reference for the use of ketamine infusion, and developing clinical pathways in the treatment of children with sickle crisis pain (Ender et al., 2014; Hagedorn & Monico, 2016; National Heart, Lung, Blood Institute, 2014; World Health Organization, 2012). These guidelines address time to initial dose of medication, opioids as the drug of choice, reassessment intervals, incorporation of technology, and intercollaborative teams. The nhlbi digital resource obtained data for a report based on consensus from the American Pain Society. Of the nine pharmacological recommendations, only one had high quality evidence and strong recommendation for rapid initiation of parental opioids for the treatment of sickle cell crisis pain; two had low quality for treatment with NSAIDs for mild pain if not contraindicated. The WHO developed a two-step approach in the pain management of pain in children with medical illnesses, after removing codeine from the analgesic ladder related to many poor metabolizers resulting in the ineffectiveness of pain relief or ultra-metabolizers resulting in toxicity. This approach recommends NSAIDs for mild pain as the first step, progressing to low-dose morphine for moderate pain, and increasing to standard dosing of morphine for severe pain. The WHO standard of pain assessment is, upon arrival at emergency department with administration of parental opioid, with 30 minutes of triage or 60 minutes of registration, and with subsequent pain assessment at 15-30-minute intervals until pain is controlled, as reported by the patient. All the guidelines and reviews agree that morphine is an essential medication in the treatment of sickle cell crisis pain. In patients with repeated failed pain relief with opioids and NSAIDs, the addition of non-opioids and adjuvant may significantly decrease pain scores.

Managing pediatric sickle cell crisis pain is resource and time intensive. Only 9% of pediatric-trained and 20% of adult-trained pediatric emergency department physicians report following institutional protocols when treating sickle cell crisis pain (Cacciotti et al., 2017). Many physicians cite two factors causing delays in the treatment of pediatric sickle cell crisis pain:

1. Time required in reviewing patient chart;
2. Deciding the optimal pain management regimen.

No universal pediatric emergency department analgesic guidelines exist for the treatment of sickle cell crisis pain (Cacciotti et al., 2017). The development of multidisciplinary clinical pathways may promote the use of new knowledge in the clinical setting.

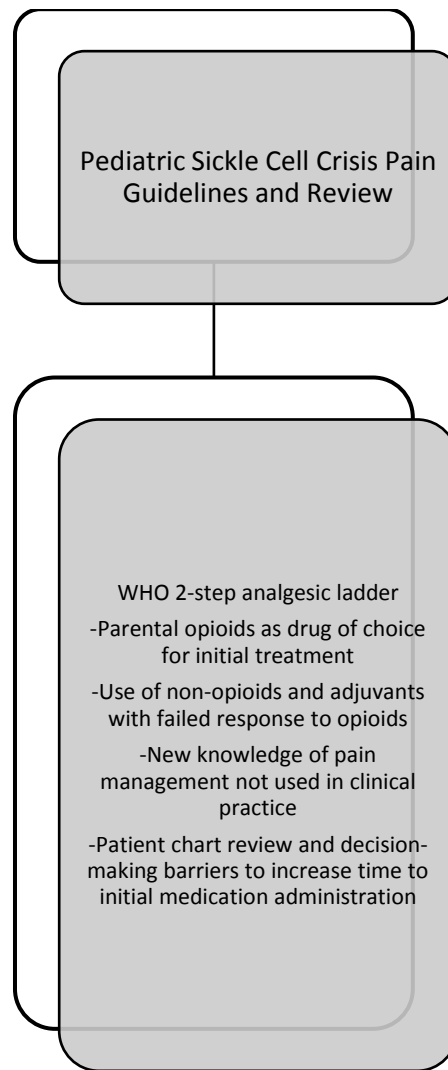


Figure 4. Flowchart of pediatric sickle cell crisis pain guideline themes. Adapted from Ender et al., 2014; Hagedorn and Monico, 2016; National Heart, Lung, and Blood Institute, 2014; World Health Organization, 2012.

Pain Management and Pediatric Sickle Cell Pain Research Trials

What identified evidence-based pain management strategies are found to be safe and effective in the hospitalized pediatric sickle cell patients in pain crisis?

Prior research generally confirms morphine as the drug of choice in the initial treatment of sickle cell crisis pain. Current research favors combination therapy of opioids and non-

steroidal medication after an initial dose of parental opioids (Badaki-Makun et al., 2014; Brandow et al., 2016; Brousseau et al., 2015; Cacciotti et al., 2017; Fein et al., 2017; Horst et al., 2016; Morris et al., 2013; Neri et al., 2013; Nottage et al., 2016; Sheehy et al., 2015; Sheehy et al., 2017). Since sickle cell crisis pain encompasses inflammatory, infarction, tissue damage, and neuropathic pain, the combination therapy of opioids, NSAIDs, and adjuvants is used to optimize pain management.

Further studies are entertaining combination therapies utilizing pathophysiology of sickle cell crisis pain and receptors, reducing opioid tolerance and opioid induced hyperalgesia. Medications not dependent on CYP2D6 pathways are needed for repeat failed opioid therapy when aberrant genetics are present. Adjuvants such as arginine, ketamine, gabapentin, fentanyl, dexmedetomidine, methadone, and magnesium are thought to be opioid reducing and safe in the hospital setting, providing analgesia in the brain and spinal cord. The route of medication administration affects the time to initial medication, and thus intranasal and subcutaneous routes are explored since intravenous access poses a delay in beginning treatment.

What factors contribute to the paucity of literature in the treatment of pediatric sickle cell pain crisis?

Much of the research in surrounding pediatric sickle cell crisis pain is hindered by the inability to obtain adequate sample size to conduct research with generalizable results. The most common limiting factor in completing research trials among this population relates to patients presenting to the emergency department in distress, hindering their ability to give consent/assent. Many research designs are shifting to obtaining consent/assent during routine clinic visits, in order to increase participation for outcome analysis and clinical relevance.

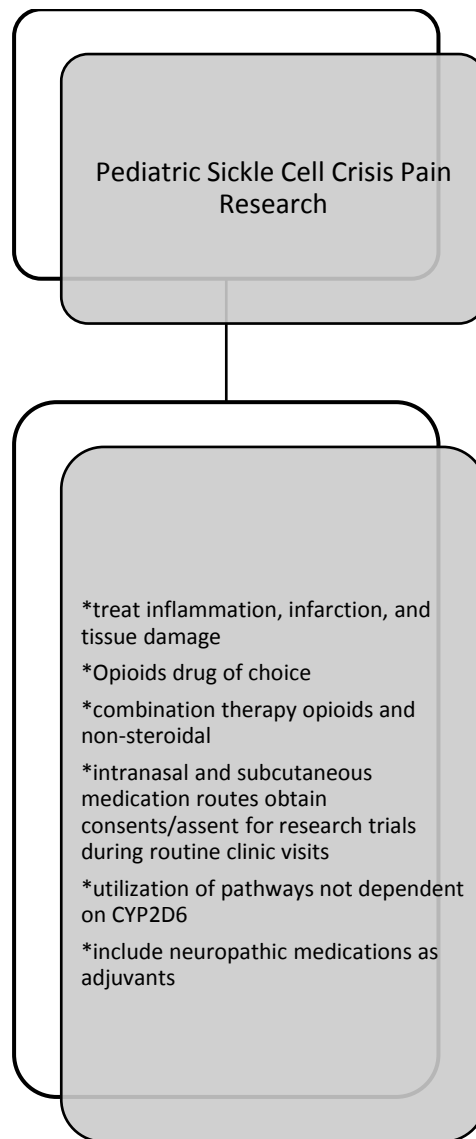


Figure 5. Flowchart of pediatric sickle cell crisis pain disease research themes. Adapted from Badaki-Makun et al., 2014; Brandow et al., 2016; Brousseau et al., 2015; Cacciotti et al., 2017; Fein et al., 2017; Horst et al., 2016; Morris et al., 2013; Neri et al., 2013; Nottage et al., 2016; Sheehy et al., 2015; Sheehy et al., 2017.

Synthesis of Results

The many advances in the care of sickle cell disease have brought only minimal improvements in the treatment of sickle cell crisis pain. The strength of the evidence was on both

ends of the spectrum, with 12 studies on the high end and nine on the moderate-to-low end on the Nursing: Melnyk Pyramid with a leveling system of I-VII. Three of the studies were reviews of one multicenter trial on magnesium in the treatment of sickle cell crisis pain with the potential to alter the pathophysiology of pain crisis. Many of the studies specific to pediatric sickle cell crisis pain had small sample sizes, closed, or were still in progress after two years seeking to obtain participants to continue the study. Many studies had small sample sizes and multicenter studies were few. Results of these studies strongly correlate patient reports of sickle cell crisis pain severity with increased risk of mortality. Many of the reviews are based on studies conducted within cancer treatment of pain and perioperative pain management disciplines. Sickle cell crisis pain is multidimensional and complex, including inflammatory, infarction, and tissue damage with a profound effect on morbidity and mortality in the pediatric population. Three major classes of medications—opioids, non-opioids, and adjuvants—are effectively used in the treatment of pediatric sickle cell crisis pain.

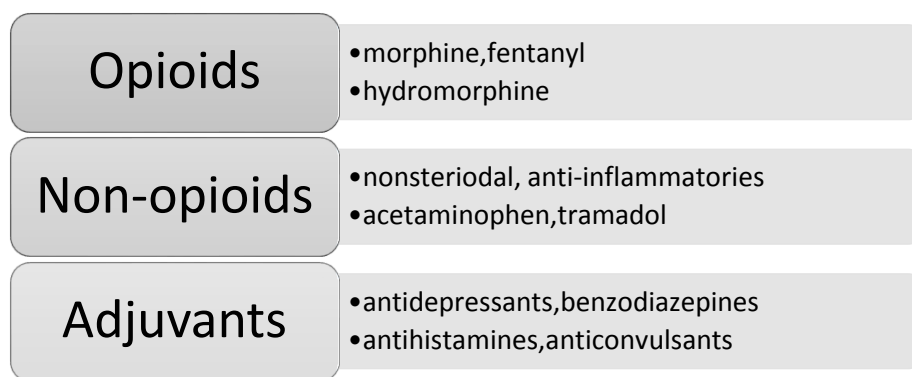


Figure 6. Flowchart of classes of safe and effective medications. Adapted from Hagedorn and Monico, 2016.

Pediatric sickle cell crisis pain research continues to depend on consensus and expert opinion with few strong research studies conducted to completion. The need to develop research

protocols that remove barriers to conducting research to completion are drastically needed. The lack of clinical guidelines utilizing new knowledge of the pathophysiology and pharmacogenomics of sickle cell crisis pain has resulted in readmission of patients presenting with the most common symptom of sickle cell disease.

Development of comprehensive emergency department guidelines with the participation of pain management, anesthesia, pharmacy, and nursing may contribute to optimal and consistent care (Badaki-Makun et al., 2014; Cacciotti et al., 2017).

Discussion

Summary of the Evidence

Research revealed the treatment of pediatric sickle cell crisis guidelines are based on few evidenced-based studies with strong to moderate recommendations based on consensus and expert opinion (National Heart, Lung, and Blood Institute, 2014; World Health Organization, 2012). The goal of this integrative review was to identify strong evidence-based studies in the pharmacological treatment of pediatric sickle cell crisis pain to bring new knowledge to clinical practice although there was strong consensus the research trials lacked sufficient numbers to apply to the general population. Many of the studies addressed the clinical question but lacked the rigor necessary to address pediatric sickle cell crisis pain management in a generalizable setting. Two of the studies discussed developing clinical pathways and individual treatment plans utilizing interdisciplinary teams and resource nurses to address the multifactorial needs of this patient population, with the understanding that only 9% of pediatric-trained and 20% of adult-trained emergency department healthcare providers utilize these important tools in improving patient outcomes (Cacciotti et al., 2017; Ender et al., 2014; Krishnamurti et al., 2014). Although the 21 studies addressed pharmacological management of sickle cell crisis pain, three studies

included new knowledge from pathophysiology and pharmacogenomics in their studies (Brousseau et al., 2015; Jaja et al., 2014; Neri et al., 2013). Since mechanism-based strategies for treating sickle cell crisis pain are sorely lacking, healthcare providers are reduced to treating the symptom of pain (Sheehy et al., 2015).

Limitations

According to Cooper (1982), the five stages in the integrative review process are to provide rigor and address threats in the review (Cooper, 1982). External bias of the studies related to small sample size and single institution subjects was observed. Since inclusion criteria were limited to U.S. studies, the strength of the evidence with combined studies was lacking. Another limiting factor during the data evaluation stage was the use of one reviewer, who was also the project leader.

Additional research is needed with larger sample sizes and multicenter involvement to address the treatment of sickle cell crisis pain utilizing pathophysiology and pharmacogenomics in the process. Research teams need to be more interdisciplinary and intercollaborative, including all stakeholders to address this most debilitating problem in the lives of children with sickle cell disease. The development of practice guidelines in other medical conditions has improved clinical outcomes and patient satisfaction. This is an opportunity to build upon nursing science, policy development, and applying new knowledge into clinical practice.

Conclusion

The undertreatment of sickle cell crisis pain is well known among healthcare providers caring for children with sickle cell disease. The increased cost, hospitalizations, missed school days, and decrease in life expectancy are not an option in the 21st-century healthcare environment. This integrative review seeks to raise awareness of the old but continuing saga of

undertreated pediatric sickle cell crisis pain and its effect on society, and its global impact.

Historically, patients who report high pain scores had increased risk of early death compared to patients who report lower scores. Sickle cell disease is the most common of all inherited hemoglobinopathies, with an average healthcare cost of \$1,354,000 during childhood (ages 1-21). Clinical pathways for other pediatric diseases promote rapid stabilization, reduced hospital admission rates, reduced inappropriate therapies and should be considered in addressing the undertreatment of pediatric sickle cell crisis pain. Healthcare providers are in a position to affect policy and practice changes to support clinical guidelines and research opportunities to address this age-old concern. How long must children with sickle cell disease suffer from sickle cell crisis pain? Healthcare providers must answer with a unanimous voice: “Not long.”

Implications for Practice

The most common presenting symptom of sickle cell disease to the emergency department is sickle cell crisis pain in children, and it remains the most resource- and cost-intensive medical illness. There is a great need to develop guidelines to decrease pain frequency and intensity based on high quality evidence-based research. The addition of information technology with the ability to create reminders in medication administration to assist providers in busy emergency departments and to allow easy access to protocols to facilitate decision making regarding treatment regimens is desperately needed. Enhancing healthcare providers’ knowledge of effective treatment strategies and new knowledge from pathophysiology and pharmacogenomics is paramount in the care of children experiencing sickle cell crisis pain. The development of point-of-care genomic testing for individuals with repeated pharmacological failures is a valuable tool to direct effective evidence-based pain management in this patient population.

Research supports the use of opioids, non-opioids, non-steroidal pain relievers and adjuvants in the treatment of sickle cell crisis pain with the introduction of intranasal and subcutaneous routes when there is a delay in obtaining intravenous access. More research in the study of medications addressing the pathophysiology of sickle cell crisis pain is needed, with access to identifying repeat failures of opioid and NSAID treatment in this patient population. Healthcare providers need to address the multidimensional elements in developing evidenced-based, individualized strategies in the treatment of pediatric sickle cell crisis pain in the hospital setting.

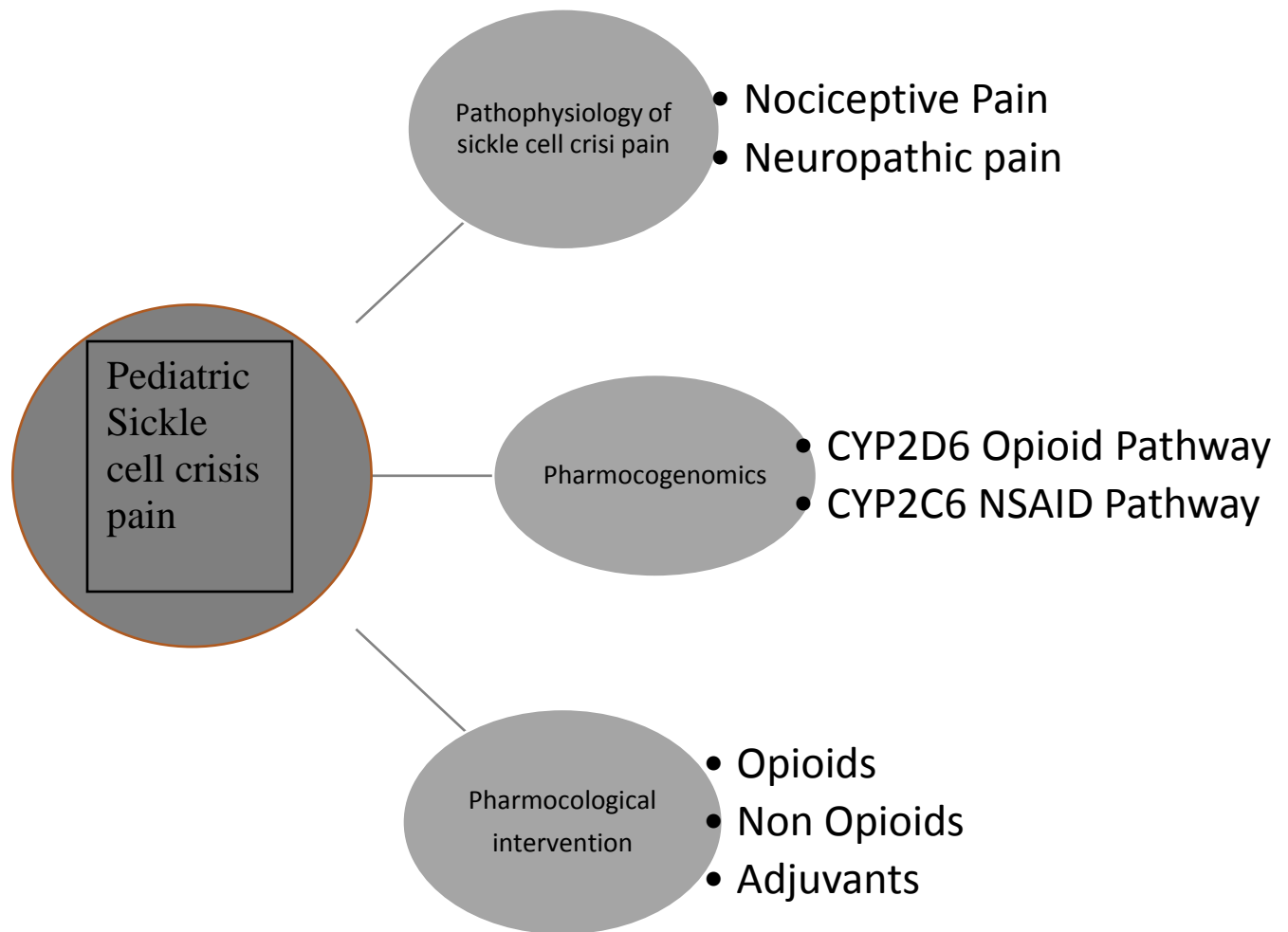


Figure 7. Flowchart of multidimensional components in the treatment of pediatric sickle cell crisis pain. Adapted from Ballas, 2014; Hagedorn and Monico, 2016; Jaja et al., 2014; Nottage et al. 2016; Raphael et al., 2013; Yee et al., 2013;

Implications for Research

The major impediment in the development of generalizable evidence-based safe and effective pharmacological intervention of pediatric sickle cell crisis pain is study designs that lack adequate sample size. The inability to obtain larger sample sizes and multicenter trials leads to inferences and inappropriate treatment of children with sickle cell crisis pain. Obtaining consent and assent during the time of patient distress has been inadequate, leading to minimal participation. The development of study designs in which participation is discussed and consent/assent obtained, with a method to identify participants upon arrival at the hospital setting, has the potential of increasing participation when patient distress from sickle cell crisis pain is not a factor in the decision.

Dissemination

The purpose of this integrative review of the pharmacological pain management of pediatric sickle cell crisis pain was to provide a systematic review of separate evidence-based findings in a format to define the state of knowledge. The public presentation of the summation of accumulated knowledge concerning the pharmacological pain management of pediatric sickle cell crisis pain will utilize the internal organization pain service and poster presentation at the annual hospital nursing research symposium for 2019. Development of a manuscript for publication in a professional nursing journal is in progress.

DNP ESSENTIALS

Essential I

The DNP scholarly project assisted in enhancing nursing knowledge in understanding the impact of under-treatment of pediatric sickle cell pain crisis and the processes needed to affect positive changes in the pain experience of such patients. The utilization of *Essential I*

incorporated scientific knowledge and expert opinions from other sciences in collaboration with nursing midrange theory of symptom management in decreasing the intensity, frequency, and episodes of sickle cell pain crisis (Smith & Lieher, 2014). The integrative review, a form of systematic review, is “the strongest level of evidence to guide intervention for clinical practice” (Fineout-Overholt et al., 2005, p. 336) allowing nursing at the practice level to incorporate evidence-based practice in the care of children with sickle cell pain crisis. The project encourages discussion among stakeholders in collaboration across all entries into the healthcare system in the effective management of sickle cell pain crisis in children. The DNP is positioned to mentor nurses in the evidence-based practice process facilitating shorter intervals between research, policy, and patient care.

Essential VIII

This prepares the DNP project leader to facilitate participation in evidence-based management of pediatric sickle cell crisis pain among patients, families, nursing, and other healthcare providers sustaining therapeutic relationships to facilitate improved patient outcomes and satisfaction. *Essential VIII* focus on equipping DNP graduates in the mastery of comprehensive, systematic health assessments designing, implementing, and evaluating interventions based on nursing science and other sciences (American Association of Colleges of Nursing, 2006). Children experiencing sickle cell crisis pain enter the healthcare system at a variety of entry points of care and hours of operation, necessitating the need of effective communication within the complex healthcare system. The project will give advance practice nurses and nurses practicing in rural areas the knowledge needed to manage children experiencing sickle cell pain crisis, using evidence-based guidelines to develop specific treatment regimens according to resources, improving outcomes and providing quality patient

care. The rigor of the integrative five-step review process by Harris Cooper (1982) assists in the translation of research into practice and provides the framework to redesign effective and realistic pain management strategies in the care of children with sickle cell crisis pain.

Continuing to analyze the research for the prevention of the pain cycle in this patient population is crucial in reducing the risk of morbidity, mortality, and premature death in which the skills of the DNP as a leader and mentor are much needed in advancing nursing practice and the nursing profession.

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Table 1

Levels of Evidence for Project Literature Reference

Evidence category	Numeric level	Number of articles for project
Systematic review & meta-analysis of randomized controlled guidelines	1	2
One or more randomized controlled trials	2	7
Controlled trial (no randomization)	3	1
Case-control or cohort study	4	0
Systematic review of descriptive & qualitative studies	5	3
Single descriptive or qualitative study	6	6
Expert opinion	7	1

Table 2

Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Dates 2012 to 2017	Dates prior to 2012
Children ages 0 years to 21 years	Children older than 21 years
Full text articles	Abstract only articles
Studies performed in the U.S.; Peer-reviewed articles at all levels per Melnyk Levels of Evidence (2015)	Studies outside of the U.S.
English language	Non-English languages
Pharmacological pain management therapies	Non-pharmacological, complementary, and alternative therapies

Table 3

Results Matrix for Pain and Pediatric Sickle Cell Disease

Focus of Article, Author, and Year	Critique: Level of Evidence and Source	Pediatric Sickle Cell Pain/Background	Conclusions	Practice Implications and Recommendations
Principles of vaso-occlusive crisis management and pharmacogenomics of opioids (Ballas, 2014)	Level 5: Systematic review of descriptive and qualitative studies	<ul style="list-style-type: none"> Healthcare providers' knowledge of sickle cell pain management was suboptimal in the 1950's-1970's. Many people with sickle cell disease died during childhood and young adulthood. Recent life expectancy ranges from 50-70 years. Chronic pain is more common and severe. Dorsal horn is main pathway to central 	<ul style="list-style-type: none"> Opioids are the most commonly used analgesic in the management of sickle cell pain. Gap between new advances in pathophysiology of pain, pharmacogenomics of opioids, and the clinical management of sickle cell pain The pathophysiologic mechanism of sickle cell vaso occlusive crisis varies depending on the clinical presentation. Specific analgesics should be aligned with the specific 	<ul style="list-style-type: none"> Understanding of the pathophysiologic mechanism of pain and pharmacogenomics of opioids has improved significantly. Clinical management of sickle cell pain does not reflect new knowledge. <p>Recommendations</p> <ul style="list-style-type: none"> Determine analgesics in alignment with specific pathophysiologic mechanism and pharmacogenomics of opioids. Clinical trials to determine clinical

		<p>nervous system pain relief efforts by the endogenous endorphins.</p> <ul style="list-style-type: none">• Two Na⁺ channels receptors (α-Amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-Daspartic acid (NMDA) which determine the type, severity, and duration of vaso-occlusive pain crisis• The AMPA and NMDA allow for effective pain relief with non-opioids and opioids unless	<p>pathophysiologic mechanism and pharmacogenomics of opioids.</p>	<p>efficacy of opioids and CYP genotypes in patients with sickle cell pain.</p>
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		<p>aberrant. metabolism exist</p> <ul style="list-style-type: none"> • With the many advances in treating sickle cell disease minimal advances in management sickle cell pain are noted. 		
<p>The focus of this study is to determine the frequency of CYP2C9 alleles and genotypes in children with sickle cell disease in the U.S. and African American populations (Jaja et al., 2014).</p>	<p>Level 2: Randomized controlled trial</p>	<ul style="list-style-type: none"> • GI complications, renal impairment, fluid retention, asthma exacerbation are some of the adverse effects associated with impaired NSAID metabolism. 	<ul style="list-style-type: none"> • Study showed 30% of subjects with at least one allele associated with reduced function in metabolizing NSAIDS. • Sickle cell disease patients have a slightly higher frequency of the CYP2D6 gene deletions compared to healthy African Americans related to opioid conversion. • NSAIDs are the 	<ul style="list-style-type: none"> • Inform genomic-based drug prescribing practice • The CYP2C9 variants play an important role in the analgesic effect and toxicity of NSAIDS. <p>Recommendations</p> <ul style="list-style-type: none"> • Preemptive genotyping would provide explanation for those individuals with unsatisfactory drug

			backbone of pain management of children with sickle cell disease.	<p>response or side effects profiles enabling clinicians to make distinctions between a compliance problem and a metabolic defect.</p> <ul style="list-style-type: none"> • Future studies to determine the CYP2C9 profiles of sickle cell disease patients that could potentially enable clinicians to identify patients with impaired CYP2C9 metabolic capacity and tailor NSAIDs dosing accordingly to achieve optimal analgesic response.
The focus of this study is to determine the frequency of CYP2D6 alleles and genotypes in children	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> • For codeine and hydrocodone CYP2D6 is the first step in the 	<ul style="list-style-type: none"> • Morphine clearance is significantly higher in patients with sickle cell disease compared 	<ul style="list-style-type: none"> • Sickle cell disease patients may require higher and more frequent opioid doses to

<p>with sickle cell disease in the U.S. and African American populations (Yee et. al, 2013).</p>		<p>pathway of opioid analgesic effect, converting the prodrug to morphine or hydromorphone respectively.</p> <ul style="list-style-type: none"> • CYP2D6 testing should be considered in patients with repeated failed outpatient pain management. • Opioid medications such as morphine or hydromorphone that do not require enzymatic activation may produce better analgesia in this patient population. 	<p>to non-sickle cell disease individuals.</p> <ul style="list-style-type: none"> • Limitation includes the inability to identify less common CYP2D6 alleles. 	<p>maintain adequate analgesia.</p> <ul style="list-style-type: none"> • Genetic variations in the CYP2D6 gene may contribute to poor responses to common pain medications for outpatient sickle cell pain management. • Personalized medicine along with genetic testing will assist clinicians to predict response to medications and tailor treatments-based on genetic polymorphisms. <p>Recommendations</p> <ul style="list-style-type: none"> • Larger studies of CYP2D6 genotypes need to be accomplished. • Further study of the extent of CYP2D6
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				contribution to failed outpatient pain management among sickle cell disease in children
Determine whether administrative data have the capacity to fully assess health care utilization among children with sickle cell disease (Raphael, 2013).	Level 6: Single descriptive study	<ul style="list-style-type: none"> The average medical fee for a child with sickle cell disease during childhood ages 1-18 years is approximately 1,354,000 U.S. dollars. 	<ul style="list-style-type: none"> Administrative claims data provided key insights into the scope of health services use including how and where services are being used and highlights the limitations of sole reliance on Medicaid record reviews. 	<ul style="list-style-type: none"> Despite progress in the evaluation and management of sickle cell disease care of affected children, this medical illness continues to be a high-cost and resource-intensive disease. <p>Recommendation</p> <ul style="list-style-type: none"> Development of guidelines to decrease pain frequency and intensity Enhance provider knowledge of effective pain treatment modalities High quality research

				<p>development to provide evidence-based treatment regimens</p> <ul style="list-style-type: none"> • Development of intercollaborative teams with appropriate stakeholders
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Table 4

Result Matrix Pain Management and Sickle Cell Pain Guidelines and Reviews

Focus of Article, Author, and Year	Critique: Level of Evidence and Source	Sickle Cell Pain Guidelines and Reviews/Background	Conclusions	Practice Implications and Recommendations
The focus of this article is to provide a digital resource of the treatment recommendations extracted from the full report in the evidence-based treatment of sickle cell disease (National Heart, Lung, Blood Institute, 2014).	Level 7: Expert panel	<ul style="list-style-type: none"> • Of the 17 recommendations, 9 recommendations are related to the pharmacological treatment of vaso-occlusive pain, and 10 recommendations are related to 	<ul style="list-style-type: none"> • The range of panel expert consensus included initiation of analgesic within 30 minutes of triage or 60 minutes of registration, basing analgesic use on pain 	<ul style="list-style-type: none"> • For severe pain, consider escalation of the opioid dose by 25% until pain control. • To prevent over sedation, consider the need of long-acting opioids with continuous PCA opioid use.

		<p>assessment, hydration, blood transfusion, oxygen therapy, and non-pharmacological treatment</p> <ul style="list-style-type: none"> • Of the 9 pharmacological recommendations, a majority of the evidence was based on consensus consisting of the American pain society with evidenced reviewed by the methodology team of panel of experts. • Of the 9 recommendations only 1 had high-quality evidence and strong 	<p>assessment and patient past use of analgesic with relief of pain symptom.</p>	<p>Recommendations</p> <ul style="list-style-type: none"> • Use subcutaneous route of medication administration when intravenous access is difficult. • For severe pain, reassess every 15-30 minutes until pain is under control per patient report. • When using PCA on demand consider long-acting opioids • Do not use meperidine unless it is the only effective opioid for the individual. • Gradual titration of parenteral opioids as sickle cell disease crisis pain resolves.
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		<p>recommendation associated with rapid initiation of parenteral opioids for the treatment of sickle cell disease crisis pain.</p> <ul style="list-style-type: none">• 2 low quality evidences, moderate recommendations associated with treatment of NSAIDS for mild to moderate pain in the absence of contraindications and around the clock continuous infusion of opioids utilizing PCA versus prn administration		
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		<ul style="list-style-type: none"> • 6 recommendations were of consensus and panel expertise. 		
<p>The focus of this guideline is to provide evidence-based recommendations for the treatment of pain including opioids, non-opioids, and adjuvant medications to improve the management of pain in children experiencing pain related to medical diseases (World Health Organization, 2012).</p>	Level 7: Expert panel	<ul style="list-style-type: none"> • Low quality of evidence, strong recommendation for strong opioids as an essential medication in the treatment of sickle cell disease pain • There is no other class of medication than strong opioids that is effective in the treatment of moderate to severe sickle cell disease pain. • Acute pain is a sudden onset felt immediately 	<ul style="list-style-type: none"> • Development of a 2-step approach incorporating dosing at regular intervals, using appropriate route of medication administration, and adapting treatment to individual child • 2 step approaches are a revision of the 3-step analgesic ladder of 1986, which recommended use of codeine as a weak opioid while the 2-step approach considers low doses of strong 	<ul style="list-style-type: none"> • The effectiveness of codeine is in question related to the percentage of poor metabolizers resulting in the effectiveness of this medication. • There is no available evidence of the comparative effectiveness and safety of Tramadol in children, no license for pediatric use in several countries and more research needed. • Steroids (corticosteroids) and bisphosphonates (bone pain) are

		<p>following injury, severe in intensity, arises because of tissue injury stimulating nociceptors and generally disappears when injury heals.</p> <ul style="list-style-type: none"> • Sickle cell disease pain is generally nociceptive superficial and deep somatic visceral pain arising from internal organs, bones, joints, muscles, connective tissue, nose, urethra, anus, skin, and nose. • Sickle cell disease arms, legs, abdomen, chest, and back 	<p>opioids for the treatment of moderate pain</p> <ul style="list-style-type: none"> • 2-step strategy strong recommendation with very low quality of evidence 	<p>not recommended as adjuvants in the treatment of sickle cell disease pain in children.</p> <ul style="list-style-type: none"> • At the time of this guideline not possible to make recommendations because of limited studies on the use of gabapentin and sub-anesthetic dose of ketamine • Fear and lack of knowledge are a barrier to the relief of pain using opioids in children. • The World Health Organization included morphine as an essential medication in the treatment of pain in children. • No evidence among children or
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		pain generally last 4-5 days.		<p>adults to recommend opioid rotation to prevent side effects of dose escalation.</p> <p>Recommendations</p> <ul style="list-style-type: none">• Utilize 2-step strategy in the treatment of sickle cell disease pain in children.• First step is the treatment of mild pain with paracetamol and ibuprofen, a strong recommendation with low quality evidence.• Second step is the treatment of moderate to severe pain with morphine as the drug of choice.• Medication should be administered at
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				<p>regular intervals using the appropriate route of administration, adapting the treatment to the individual child.</p> <ul style="list-style-type: none"> • Adjuvant medicines may be co-administered with analgesic to enhance pain relief.
<p>The focus of this article is to provide a definitive reference for the use of ketamine infusion for pain management among persons with sickle cell pain (Hagedorn & Monico, 2016).</p>	<p>Level 5: Systematic review of descriptive and qualitative studies</p>	<ul style="list-style-type: none"> • Sickle cell pain effectively managed in the emergency department and hospital using 3 major classes of medications: opioids, non-opioids, and adjuvants • Most common opioids: morphine, hydromorphone, and fentanyl. 	<ul style="list-style-type: none"> • Ketamine infusion may provide adequate pain relief for those who have failed the typical pain management regimen. • Ketamine infusions used with opioids reduce opioid usage. • Adverse effects 	<ul style="list-style-type: none"> • Ketamine may be a useful adjuvant with opioid when high doses result in no analgesic effect. • Ketamine infusions are to be performed in the hospital setting where adverse reactions can be managed. <p>Recommendations</p> <ul style="list-style-type: none"> • No specific

		<ul style="list-style-type: none">• Non-opioid medications include nonsteroidal, anti-inflammatories, acetaminophen, and tramadol.• Adjuvant medications include antidepressants, benzodiazepines, antihistamines, and anticonvulsants.• Non-pharmacological therapies include psychological evaluation; occupational, behavioral, and cognitive therapy; acupuncture; exercise; massage; and	were hypertension, unresponsiveness, nystagmus, and dysphoria.	<p>recommendations can be made until further studies are performed using Ketamine infusions among pediatric patients with sickle cell pain.</p> <ul style="list-style-type: none">• Ketamine infusions may be useful in treating pediatric sickle cell pain refractory to other standard treatment.
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		aqua therapy.		
The focus of this article is to determine prospectively whether a clinical pathway improves the acute management of sickle cell disease vaso-occlusive pain in the pediatric emergency department (Ender, 2014).	Level 3: Control trial, no randomization	<ul style="list-style-type: none"> • Inadequate treatment of pain is associated with fatal complications such as acute chest syndrome. • Patients with highest pain scores have historically had increased risk of early death compared to those with the lowest pain scores. • Clinical pathways for other pediatric diseases than sickle cell disease have shown to promote more rapid stabilization, decrease 	<ul style="list-style-type: none"> • Clinical pathways can improve important aspects of pain management such as time to first analgesic, time to first opioid, increased use of ketorolac. There was no significant change in pain scores. 	<ul style="list-style-type: none"> • Clinical pathways in children with sickle cell disease will need to address multifactorial causes of pain and treatment strategies. <p>Recommendations</p> <ul style="list-style-type: none"> • Further studies on developing clinical pathways with multidisciplinary teams including emergency department physicians, hematology physicians, pharmacists, nursing, and patient/families.

		hospital admission rates, and reduce the use of inappropriate therapies.		
Individualized pain management plans developed because of successful implementation of a standard protocol jointly by the emergency department physician and primary hematologist improve patient satisfaction with pain management and reduce hospital admissions as well as readmission rates (Krishnamurti, 2014).	Level 6: Single descriptive study	<ul style="list-style-type: none"> Algorithm emphasized early initiation of treatment with intravenous morphine of hydromorphone with the goal of obtaining significant pain relief within 1-2 hours of arrival at the emergency department. 	<ul style="list-style-type: none"> Study demonstrated that detailed individualized pain management plans implemented in collaboration between the patient, hematologist, and emergency department staff can improve management of sickle cell associated vaso-occlusive crisis in the emergency department. 	<ul style="list-style-type: none"> Project compared admission and readmission rates within a week and average length of hospital stay. Reduction in length of hospital time served as an indicator of effective pain management in the emergency department as well as during hospitalizations. <p>Recommendations</p> <ul style="list-style-type: none"> Each plan included a list of current home medications, other medications, analgesic dosage, and frequency of

				<p>administration for emergency department care and inpatient pain medication regimen.</p> <ul style="list-style-type: none"> • Sickle cell nurse coordinator visited each patient during weekday daytime hours and supported emergency department staff. • After hours emergency department staff interacted with hematology/oncology fellow on call.
Identify factors associated with delays in treatment of sickle cell disease pain crisis in the emergency department with goal of discerning whether earlier pain management is	Level 6: Single descriptive study	<ul style="list-style-type: none"> • The number of people with sickle cell disease is estimated to be 72,000 to 98,000 when corrected for 	<ul style="list-style-type: none"> • Patient experienced significant delays to initial analgesic medications. 	<ul style="list-style-type: none"> • A standardized approach to pain management may improve emergency department management of sickle cell disease

<p>correlated with better clinical outcomes (Lin, 2016).</p>		<p>early mortality.</p> <ul style="list-style-type: none"> • Sickle cell disease patients have highest pain scores of all emergency department diagnosis, with a mean score of 8.7 of 10. • Leading causes of mortality include bacterial infections from encapsulated organisms at 38%, cerebral vascular accidents at 12.3%, and acute pain episodes and acute chest syndrome at 11%. • Opioids are most common initial pain medication 		<p>pain crisis.</p> <ul style="list-style-type: none"> • Improved pain management may help prevent admissions from sickle cell pain and may decrease acute chest syndrome and mortality from sickle cell disease. <p>Recommendations</p> <ul style="list-style-type: none"> • Management of severe pain primarily with opioids with potential addition from classes of analgesics and adjuvants • Other classes of analgesics include NSAIDs, topical agents, corticosteroids. • Adjuvants including antihistamines, benzodiazepines,
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		<p>prescribed and administered.</p> <ul style="list-style-type: none">• Second most common medications prescribed and administered are NSAIDS, most common ketorolac as initial therapy with 60% receiving opioids.• 9% of pediatric emergency department physicians report following an institutional protocol when treating pain due to sickle cell disease.• 2 factors causing delays include time required in reviewing		<p>antidepressants, anticonvulsants, and phenothiazines may enhance the analgesic potential and ameliorate potential adverse effects.</p> <ul style="list-style-type: none">• Future use of electronic ordering system alerting provider when a patient had not received first medication dose
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		patient chart and deciding optimal pain management regimens.		
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Table 5

Results Matrix for Pain Management and Sickle Cell Pain Research Trials

Focus of Article, Author, and Year	Critique: Level of Evidence and Source	Research Trials/Background	Conclusions	Practice Implications and Recommendations
Arginine as a safe and inexpensive, and narcotic-sparing intervention in the treatment of sickle cell pain in children (Morris, et, al., 2013)	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> Arginine is an obligate substrate for nitrous oxide production, and acute deficiency is associated with pain. Single center, prospective, randomized, double-blinded, placebo-controlled trial 38 patients ages 3-19 years with an average age of 13.9 +/- 4 years 	<ul style="list-style-type: none"> No significant difference in length of hospital stay between arginine and placebo group 54% reduction in opioid use in the arginine group during hospitalization Pain scores at discharge in the arginine group were significantly lower than the placebo group. 	<ul style="list-style-type: none"> No safety concerns have emerged with arginine use. Patients prefer IV instead of oral administration of arginine. Reduction in opioid use by 54% Beneficial adjunct to standard therapy <p>Recommendations</p> <ul style="list-style-type: none"> Multicenter trial with larger cohort

				<ul style="list-style-type: none"> • Multicenter trial with cross-over during hospitalization
Evaluate methadone pharmacokinetics in children and adults with sickle cell disease with secondary aim to assess pain relief and opioid consumption (Horst, 2015).	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> • Morphine is the opioid most commonly used to treat pain associated with sickle cell disease and is the only opioid with previously defined intravenous pharmacokinetics in children with sickle cell disease. • Methadone may have several therapeutic advantages compared with morphine, including a more rapid onset of effect, longer elimination half-life and duration of effect, greater bioavailability, and absence of active metabolites. 	<ul style="list-style-type: none"> • Methadone produced more pain relief than standard care in children with sickle cell disease. • Higher plasma concentrations of S-methadone and faster systemic elimination of S-methadone comparable with children receiving IV methadone during major surgery • Sickle cell disease does not alter the pharmacokinetics of methadone in children. • Pain relief scores at baseline did not differ, but pain relief was significantly greater at 12, 24, and 	<ul style="list-style-type: none"> • Morphine may not be optimal choice as it has an increased clearance and shorter half-life in patients with sickle cell disease, resulting in increasing doses to achieve analgesia. • Morphine used in sickle cell disease has also been associated with an increased risk of acute chest syndrome compared with nalbuphine and a slower onset of pain relief compared to other

			48 hours in children receiving methadone.	<p>opioids.</p> <ul style="list-style-type: none"> • Previous pharmacokinetics of methadone parameters can be used to guide dosing in children with sickle cell disease. • Methadone, a NMDA receptor agonist, may reduce the positive feedback loop associated with hyperalgesia. <p>Recommendations</p> <ul style="list-style-type: none"> • Further evaluations of the effectiveness and safety of higher initial IV dose of methadone in children with sickle disease pain
Effects of subanesthetic Ketamine on pain intensity and opioid	Level 6: Single descriptive study	<ul style="list-style-type: none"> • Chart review of patients receiving Ketamine infusions • Included pain 	<ul style="list-style-type: none"> • Ketamine infusions safe in the hospital setting • Best results in cancer 	<ul style="list-style-type: none"> • Use in the in-patient treatment of cancer-related pain

use (Sheely et.al, 2017)		<p>diagnosis of vaso occlusive crisis and sickle cell disease</p> <ul style="list-style-type: none"> • 230 patients and 360 separate hospital admissions infusions were eligible • Greater median reductions in opioid intake with sickle cell patients and patients with malignancy-associated pain 	<p>pain</p> <ul style="list-style-type: none"> • Study does not examine effect on chronic postsurgical pain. • No control group for this study and caution needed in generalizing results 	<ul style="list-style-type: none"> • No significant psychotropic effects and hemodynamic side effects • Possible hypertension during Ketamine infusion may require vasoactive drugs. <p>Recommendations</p> <ul style="list-style-type: none"> • More clinical trials with control group
Gabapentin in the treatment of vaso-occlusive neuropathic pain (Nottage, 2016)	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> • Research concentrated on prevention of vaso-occlusive crisis with use of hemoglobin F-inducing agents, principally hydroxyurea, little effort toward investigating management of acute pain crisis in children • Allodynia and hyperalgesia are common symptoms of 	<ul style="list-style-type: none"> • This trial is open and started 2 years prior to January 2016 and will continue for 2 more years. At the end it will answer the question regarding gabapentin as an effective home use in conjunction with oral opioids and non-opioids at the time of pain onset, with the goal of reducing the 	<ul style="list-style-type: none"> • Recognition that pain is nociceptive and neuropathic • Concurrent use of morphine and gabapentin provide better analgesic at low doses than single-agent therapy. • A single high dose of gabapentin

		<p>sickle cell pain and defining characteristics of neuropathic pain.</p> <ul style="list-style-type: none"> • Opioids act on μ receptors, non-steroidal drugs inhibit cyclooxygenase, and gabapentin-related medications affect the $\alpha_2\delta$ subunit of the voltage dependent calcium channel. • Synergy of morphine and gabapentin likely result of actions on peripheral and central nervous systems • Sickle cell pain crisis is the leading cause of hospitalizations and drivers of healthcare expenditure in the sickle cell population. • Pain is addressed inadequately in most clinical settings, and current treatment strategies are unsatisfactory. 	<p>need for acute visits to the emergency department and hospitalizations for vaso-occlusive pain crisis.</p>	<p>decreases time delays to first request for analgesia, decrease pain intensity, and decrease opioid consumption</p> <p>Recommendations</p> <ul style="list-style-type: none"> • Limiting factor for completing research trials among this patient population related to patient presenting in distress hindering their ability to give consent/assent.
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		<ul style="list-style-type: none"> • Drugs targeting neuropathic pain have not been studied prospectively. 		
To determine if children with vaso-occlusive pain crisis who receive initial treatment with intranasal fentanyl compared to placebo achieve a greater decrease in pain score after 20 minutes (Fein, 2016)	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> • Pain accounts for approximately 70% of emergency department visits for children with sickle cell disease. • Delay in obtaining intravenous access in children with sickle cell disease is related to scarring of veins from frequent blood draws and prior episodes of intravenous access. • 20 minutes chosen because it corresponds to the time after peak serum concentration and the known onset of therapeutic effect of intranasal fentanyl and within the National Heart Lung 	<ul style="list-style-type: none"> • Greater decrease in pain scores at 20 minutes after administration of intranasal fentanyl 	<ul style="list-style-type: none"> • Possible that transmucosal absorption of intranasal fentanyl is different in a child with vaso-occlusive pain crisis related to microvascular congestion in the nasal capillary bed, resulting in either less drug being absorbed or needing greater time until drug absorption, thus prolonging the time of therapeutic effect • Intranasal fentanyl may serve as a noninvasive way to bridge the gap until intravenous

		<p>Blood institute recommended timeframe for reassessment of pain after analgesic administration</p> <ul style="list-style-type: none"> Intranasal medications are easily administered; rapid onset of action avoids the gastrointestinal tract and hepatic first pass metabolism and by-passes the brain-blood barrier specifically targeting the central nervous system. 		<p>access can be obtained and further parenteral analgesics can be administered.</p> <p>Recommendations</p> <ul style="list-style-type: none"> To not force decision making while under the emotional duress of a vaso-occlusive pain crisis, obtain consent/assent by pre-enrolling during outpatient hematology visit separate from pediatric emergency department visit.
Hospital case report of 3 patients who during vaso-occlusive pain crisis had severe pain unresponsive to opioids and ketamine and were	Level 6: Single descriptive study	<ul style="list-style-type: none"> Most approaches to treat sickle cell disease pain have poor levels of evidence, being based on observational studies and expert 	<ul style="list-style-type: none"> Dexmedetomidine in combination with opioid and ketamine is well tolerated and temporarily associated with reduction in opioid requirements 	<ul style="list-style-type: none"> Some sickle cell disease patients develop pulmonary hypertension, which is a known independent risk

treated with dexmedetomidine. (Sheely, 2015)		<p>opinions rather than on clinical trials.</p> <ul style="list-style-type: none"> • Providers mostly treat symptoms because mechanism-based strategies for sickle cell disease associated pain are sorely lacking. • Dexmedetomidine without respiratory depressant effect used as sedative and/or analgesic during perioperative period and intensive care units 	and improved pain scores.	<p>factor for mortality.</p> <ul style="list-style-type: none"> • Theoretical concern for vasoconstrictive effect of pulmonary vasculature <p>Recommendations</p> <ul style="list-style-type: none"> • Trained registered nurses to administer subanesthetic doses of ketamine providing monitoring of heart rate, oxygen, and blood pressure with starting ketamine dose of 0.1 mg/kg/hr. per attending physician discretion.
Low dose ketamine as an adjuvant to opioids as a therapeutic option	Level 5: Systematic review of descriptive and qualitative studies	<ul style="list-style-type: none"> • Ketamine is a non-barbiturate phencyclidine that provides analgesia in 	<ul style="list-style-type: none"> • Emerging data suggest role of N-methyl-D-aspartate (NMDA) receptor in 	<ul style="list-style-type: none"> • Ketamine has an inotropic action and induces vasoconstriction

to manage refractory sickle cell disease related pain (Neri, 2013)		<p>the brain and spinal cord.</p> <ul style="list-style-type: none"> • Modulate opioid tolerance and opioid-induced hyperalgesia • Low-dose ketamine decreases heart rate and blood pressure. • Low dose ketamine used in the management of acute post-operative pain in non-sickle cell disease patients • Few studies evaluated ketamine in sickle cell disease patients. • Most studies included small case review numbers with improved pain control and decreased morphine use after addition of ketamine. 	opioid tolerance and opioid induced hyperalgesia.	<p>by inhibiting nitrous oxide production, resulting in increased heart rate and blood pressure.</p> <ul style="list-style-type: none"> • Ketamine increases myocardial oxygen demand. <p>Recommendations</p> <ul style="list-style-type: none"> • Studies with larger numbers evaluating ketamine as adjuvant to pain management of sickle cell disease pain in children
Hypothesized that the addition of intravenous magnesium to standard therapy would shorten	Level 2: Randomized controlled trial	<ul style="list-style-type: none"> • Several multicenter trials in the setting of sickle cell pain crisis have been closed because of inadequate enrollment, making 	<ul style="list-style-type: none"> • Intravenous magnesium did not shorten length of stay, reduce opioid use, or improve quality of life in children 	<ul style="list-style-type: none"> • Oral magnesium used previously to prevent pain crisis with some preliminary success, but

<p>hospital stay, decrease opioid use, improve health-related quality of life for pediatric patient hospitalized with sickle cell disease pain crisis (Brousseau, 2015)</p>		<p>advancements in the field difficult.</p> <ul style="list-style-type: none"> • Magnesium is a known vasodilator with anti-inflammatory effects and has the potential to alter the pathophysiology of pain crisis. • 2 previous intravenous magnesium studies single institution trials. One showed shortened length of stay from 5 to 3 days and a Canadian study with no decrease in length of stay. • Oral magnesium studied in the prevention of painful crisis not the treatment of acute painful crisis • Main discharge criterion was the ability of the patient to control pain with 	<p>hospitalized for sickle cell disease pain crisis.</p>	<p>medication not well tolerated</p> <p>Recommendations</p> <ul style="list-style-type: none"> • Research trials using oral magnesium and development of a more tolerated oral formulation
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		oral opioids.		
Describe the methods of the intravenous magnesium in sickle cell vaso-occlusive crisis in the Magnesium for Children in Crisis (MAGiC) study and discuss methods used to overcome barriers (Badaki-Makun, 2014).	Level 1: Systematic review of randomized controlled guidelines	<ul style="list-style-type: none"> • Sickle cell disease is one of the most common inherited hemoglobinopathies in the world. • Most of morbidity of sickle cell disease is due to recurrent vaso-occlusive pain crisis resulting in hospitalizations and effects on quality of life. • Current management based primarily on expert opinion with evidenced-based acute management derived from small and often inadequate powered sickle cell disease specific studies or studies of non-sickle cell disease pain 	<ul style="list-style-type: none"> • Staff availability and delay in initiation of study medication was resolved by utilizing the Pediatric Emergency Care Applied Research Network (PECARN) which provided in-person emergency department coverage and on-call coverage. • Protocol related factors resolved with participation of other departments such as pain management, anesthesia, pharmacy, nursing • Patient related factors resolved with consenting patient/families during routine care in the hematology clinic 	<ul style="list-style-type: none"> • In the U.S. 18,000 hospitalizations and 75,000 hospital days are experienced annually of children with sickle cell disease. • 28% of children with sickle cell disease admitted for vaso-occlusive pain crisis are readmitted within 30 days for another crisis. <p>Recommendations</p> <ul style="list-style-type: none"> •
Adequate and timely pain management improves quality of	Level 6: Single descriptive or qualitative study	<ul style="list-style-type: none"> • Comprehensive emergency department guidelines for assessment and 	<ul style="list-style-type: none"> • Patients who receive combination treatment were less likely to be admitted from the 	<ul style="list-style-type: none"> • <p>Recommendations</p>

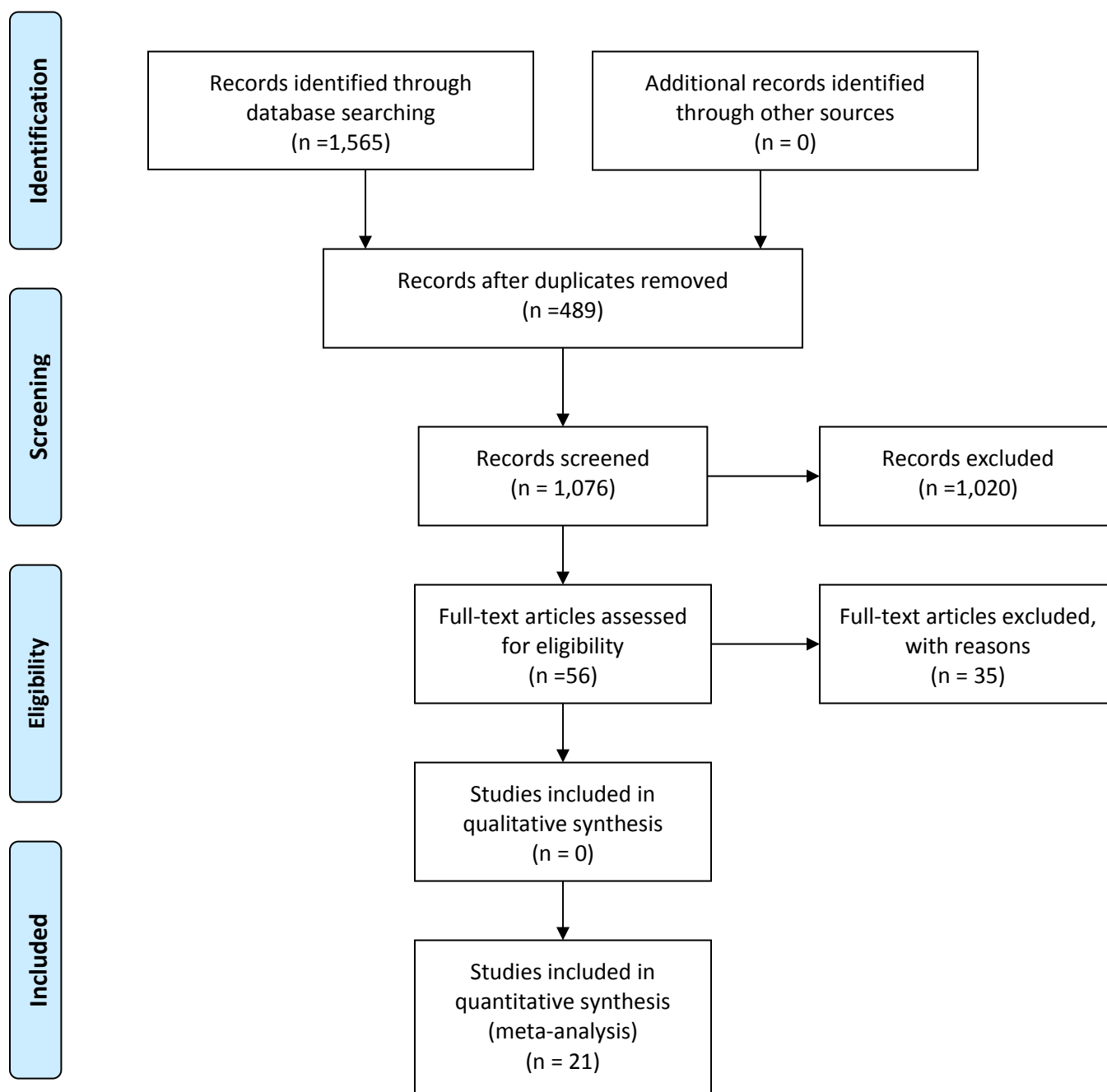
life, and rapid evaluation of pain is critical to ensure quick pain relief and prevention of complications (Cacciotti, 2017).		<p>treatment of sickle cell disease pain and may contribute to optimal and consistent care</p> <ul style="list-style-type: none"> • Pediatric emergency department analgesic guidelines for sickle cell disease pain are not universal. • Pain description: mild scale 1-3; moderate scale 4-6; severe scale 7-10 • Categories of analgesics: narcotics- morphine, Dilaudid, Percocet, or oxycodone Non-steroidal- ibuprofen, ketorolac Combination- NSAIDS and narcotics • Sickle cell pain encompasses both inflammatory and infarction and tissue damage. • In the pediatric 	emergency department for further pain management.	<ul style="list-style-type: none"> • Improved pain management may help prevent hospitalizations and morbidity associated with sickle cell disease pain. • Optimal pharmacological intervention should aim at targeting both the inflammation and tissue damage components of the pain to optimize treatment. • Combination therapy may contribute to optimizing pain management in the emergency department.
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		emergency department 20% of adult trained physicians and 9% of pediatric trained physicians report utilizing protocols when managing sickle cell related pain.		
To determine if the length of hospital stay for an acute sickle cell disease pain event is impacted by time to initiation of first intravenous narcotic at presentation, total initial dose of opioids, and or time to initiation of first oral opioid (Brandow, 2016)	Level 1: Systematic review of randomized controlled guidelines	<ul style="list-style-type: none"> • Early initiation of oral opioids facilitates transition to home pain management regimen. • Higher initial dose of opioids during early management of pain associated with improved quality of life scores at discharge 	<ul style="list-style-type: none"> • Earlier initiation of oral opioids in patients hospitalized with an acute sickle cell disease painful crisis strongly associated with shorter length of stay and improved quality of life at discharge 	<ul style="list-style-type: none"> • Early initiation of oral opioid therapy could eventually lead to standardization of treatment protocols for sickle cell disease pain. <p>Recommendations</p> <ul style="list-style-type: none"> • Collectively the existing postoperative data and findings provide rationale for future prospective trials

				regarding the effectiveness of early initiation of oral opioids.
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Appendix A

Flow Diagram



The PRISMA Statement. PLoS Med 6(7): e1000097. Doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Appendix B

CITI Training Certificate

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2 COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Brenda Middlebrooks (ID: 535011)
- **Email:** bmiddlebrooks2@liberty.edu
- **Institution Affiliation:** Liberty University (ID: 2446)
- **Institution Unit:** Nursing
- **Phone:** 770-344-7071
- **Curriculum Group:** Human subject - Basic
- **Course Learner Group:** Nursing
- **Stage:** Stage 1 - Basic Course
- **Description:** This course is appropriate for students doing class projects that qualify as "No More Than Minimal Risk" human subjects research.
- **Report ID:** 18090681
- **Completion Date:** 19-Jan-2017
- **Expiration Date:** 19-Jan-2020
- **Minimum Passing:** 80
- **Reported Score*:** 99

REQUIRED AND ELECTIVE MODULES ONLY

	DATE COMPLETED	SCORE
Belmont Report and CITI Course Introduction (ID: 1127)	29-Sep-2015	3/3 (100%)
Students In Research (ID: 1321)	08-Dec-2015	5/5 (100%)
History and Ethical Principles - SBE (ID: 490)	29-Sep-2015	5/5 (100%)
Defining Research with Human Subjects - SBE (ID: 491)	24-Jul-2007	5/5 (100%)
The Federal Regulations - SBE (ID: 502)	06-Dec-2015	5/5 (100%)
Assessing Risk - SBE (ID: 503)	06-Dec-2015	5/5 (100%)
Informed Consent - SBE (ID: 504)	06-Dec-2015	5/5 (100%)
Privacy and Confidentiality - SBE (ID: 505)	06-Dec-2015	5/5 (100%)
Records-Based Research (ID: 5)	06-Dec-2015	3/3 (100%)
Populations In Research Requiring Additional Considerations and/or Protections (ID: 16680)	08-Dec-2015	5/5 (100%)
Vulnerable Subjects - Research Involving Prisoners (ID: 8)	08-Dec-2015	4/4 (100%)
Vulnerable Subjects - Research Involving Children (ID: 9)	06-Dec-2015	3/3 (100%)
Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates (ID: 10)	08-Dec-2015	3/3 (100%)
Research and HIPAA Privacy Protections (ID: 14)	06-Dec-2015	4/5 (80%)
Vulnerable Subjects - Research Involving Workers/Employees (ID: 483)	08-Dec-2015	4/4 (100%)
Conflicts of Interest In Research Involving Human Subjects (ID: 488)	05-Aug-2007	2/2 (100%)
Unanticipated Problems and Reporting Requirements In Social and Behavioral Research (ID: 14928)	08-Dec-2015	5/5 (100%)
Cultural Competence In Research (ID: 15166)	19-Jan-2017	5/5 (100%)
Liberty University (ID: 15111)	19-Jan-2017	No Quiz

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing Institution identified above or have been a paid independent Learner.

Verify at: www.citiprogram.org/verify/7X1eR27775-b06e-492f-a5a4-6b468bd8a0c-18090681

CITI Program

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Web: <https://www.citiprogram.org>

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2

COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- Name: Brenda Middlebrooks (ID: 535011)
- Email: bmiddlebrooks2@liberty.edu
- Institution Affiliation: Liberty University (ID: 2445)
- Institution Unit: Nursing
- Phone: 770-344-7071
- Curriculum Group: Human subject - Basic
- Course Learner Group: Nursing
- Stage: Stage 1 - Basic Course
- Description: This course is appropriate for students doing class projects that qualify as "No More Than Minimal Risk" human subjects research.
- Report ID: 18090681
- Report Date: 19-Jan-2017
- Current Score**: 99

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Students in Research (ID: 1321)	08-Dec-2015	5/5 (100%)
Liberty University (ID: 15111)	19-Jan-2017	No Quiz
History and Ethical Principles - SBE (ID: 490)	29-Sep-2015	5/5 (100%)
Defining Research with Human Subjects - SBE (ID: 491)	24-Jul-2007	5/5 (100%)
Belmont Report and CITI Course Introduction (ID: 1127)	29-Sep-2015	3/3 (100%)
Records-Based Research (ID: 5)	06-Dec-2015	3/3 (100%)
The Federal Regulations - SBE (ID: 502)	06-Dec-2015	5/5 (100%)
Assessing Risk - SBE (ID: 503)	06-Dec-2015	5/5 (100%)
Vulnerable Subjects - Research Involving Prisoners (ID: 8)	08-Dec-2015	4/4 (100%)
Informed Consent - SBE (ID: 504)	06-Dec-2015	5/5 (100%)
Vulnerable Subjects - Research Involving Children (ID: 9)	06-Dec-2015	3/3 (100%)
Privacy and Confidentiality - SBE (ID: 505)	06-Dec-2015	5/5 (100%)
Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates (ID: 10)	08-Dec-2015	3/3 (100%)
FDA-Regulated Research (ID: 12)	05-Aug-2007	5/5 (100%)
Research and HIPAA Privacy Protections (ID: 14)	06-Dec-2015	4/5 (80%)
Vulnerable Subjects - Research Involving Workers/Employees (ID: 483)	08-Dec-2015	4/4 (100%)
Unanticipated Problems and Reporting Requirements in Social and Behavioral Research (ID: 14928)	08-Dec-2015	5/5 (100%)
Conflicts of Interest in Research Involving Human Subjects (ID: 488)	05-Aug-2007	2/2 (100%)
Cultural Competence in Research (ID: 15166)	19-Jan-2017	5/5 (100%)
Populations in Research Requiring Additional Considerations and/or Protections (ID: 16680)	08-Dec-2015	5/5 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing Institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/27775-b06e-492f-a5a4-6bf468bd8a0c-18090681

Collaborative Institutional Training Initiative (CITI Program)

Email: support@citiprogram.org

Phone: 888-529-5929

Web: <https://www.citiprogram.org>

Appendix C

LIBERTY UNIVERSITY
INSTITUTIONAL REVIEW BOARD

February 26, 2018

Brenda Middlebrooks

IRB Application 3189: Pharmacological Pain Management and Pediatric Sickle Cell Crisis Pain

Dear Brenda Middlebrooks,

The Liberty University Institutional Review Board has reviewed your application in accordance with the Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations and finds your study does not classify as human subjects research. This means you may begin your research with the data safeguarding methods mentioned in your IRB application.

Your study does not classify as human subjects research because it will not involve the collection of identifiable, private information.

Please note that this decision only applies to your current research application, and any changes to your protocol must be reported to the Liberty IRB for verification of continued non-human subjects research status. You may report these changes by submitting a new application to the IRB and referencing the above IRB Application number.

If you have any questions about this determination or need assistance in identifying whether possible changes to your protocol would change your application's status, please email us at irb@liberty.edu.

Sincerely,

F

G. Michele Baker, MA, CIP
Administrative Chair of Institutional Research
The Graduate School

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