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Title Page: Improving Health Outcomes in Persons with Sickle Cell Disease

Lori L. Johnson Vick, BSN MAT

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing

2016

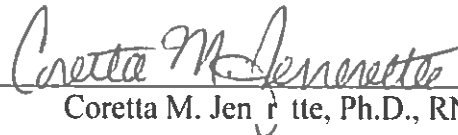
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Dedication and Acknowledgement

This compendium is dedicated to my beloved husband, Scott, and my dear children Beverly, Aaron, Richard, Donnie, Brooke, and Brittney.

I am grateful to my family, friends, and the many mentors that helped to make this journey meaningful. The author recognizes and thanks Gail W. Stuart, Ph.D., RN, FAAN, Medical University of South Carolina, for her mentorship, leadership as chair of the dissertation committee, and meticulous review of the manuscripts in this compendium. Gratitude is extended to the dissertation committee members for their support and contributions to the development of this compendium: Martina Mueller Ph.D.; Shannon Phillips Ph.D., RN, CCRN; Ron Acierno, Ph.D., Medical University of South Carolina; and Coretta Jenerette Ph.D., RN, CNE, University of North Carolina at Chapel Hill. Dr. Jenerette's research data and generosity made possible the development of the secondary analysis manuscript. The editorial support of Lori Muntz, Ph.D.; Diane J. Angelini EdD, CNM, NEA-BC, FACNM, FAAN; and Dr. John D. Dinolfo, Visiting Assistant Professor, Center for Academic Excellence & Writing Center, Medical University of South Carolina, was invaluable. Two of the manuscripts were generated in courses instructed by Carolyn M. Jenkins, DrPH, APRN, RD, LD, FAAN and Barbara J. Edlund Ph.D., APRN, ANP-BC, Medical University of South Carolina; sincere gratitude is extended for their support. The manuscript entitled "The Application of Genomic Testing for Pain Management in Sickle Cell Disease" is dedicated to the memory of Dr. Ida Johnson Spruill, Ph.D., RN, LISW, FAAN, Associate Professor Emerita of the College of Nursing, Medical University of South Carolina, for her support of this manuscript and encouragement of minority nursing students in pursuit of their academic goals.

Dear God, help me to continue to do Your work in this world! ~Lori L. Johnson Vick

Abstract

Purpose: The purpose of this compendium is to identify strategies that influence health outcomes of persons with sickle cell disease (SCD) by investigating available pain instruments, current use of genetic testing to personalize therapies, and the associations of psychosocial characteristics with quality of life.

Problem: Suboptimal care for patients with SCD is associated with non-comprehensive pain assessment instruments, limited use of available genetic tests to prescribe the potentially most effective pharmaceuticals in a personalized plan of care, and the absence of national evidence-based guidelines for the psychosocial care of this population.

Approach: The research designs used were an integrative review with a biopsychosocial-religiosity/spirituality (BPS-R/S) framework, a literature review using Diffusion of Innovation as a framework, and a quantitative study guided by the Theory of Self-Care Management for Sickle Cell Disease using secondary analysis.

Findings: The integrative review suggested that pain control outcomes might be improved by incorporating biopsychosocial-religiosity/spirituality measures to the pain instruments. The literature review indicated that the use of available genetic tests to determine the efficacy of pharmaceutical treatment options might lead to personalized care in the person with SCD. The secondary analysis found that the association between psychological factors and quality of life in the SCD sample was significant and suggested that randomized controlled trials be conducted to confirm findings prospectively. The overall findings identified that persons with SCD have complex needs inherent in a disease process that affects all body systems. Pain is the hallmark characteristic of the disease and is a dynamic biopsychosocial phenomenon.

Conclusion: BPS-R/S and genetic domains contribute to humanistic care and may benefit persons with SCD. Persons with SCD may experience improved health outcomes when the biopsychosocial- religiosity/spirituality dimensions are supported by services in the healthcare environment. The implementation of these findings through researcher, provider, patient, and family education may improve health outcomes and quality of life.

Key words: Pain, sickle cell, measurement, instruments, validity, biopsychosocial, religiosity, spirituality, cytochrome P450, pain, pharmacogenomics, genetics, genomics, nursing, psychosocial, mental health, secondary analysis.

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Chapter 1

Sickle Cell Compendium Introduction

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Sickle Cell Compendium Introduction

Sickle cell disease (SCD) is the most common genetic blood disorder in the United States (National Library of Medicine [NLB], 2015b). It is categorized as an autosomal recessive genetic group of disorders, with 1000 newborns diagnosed each year (Sickle Cell Disease Association of America [SCDAA], 2015). Persons with SCD are typically descendants of African, Mediterranean, Arabian, East Indian, South American, Central American, or Caribbean origin (Piel, et al., 2010; U.S. Department of Health and Human Services [USDHHS], 2011). Surveillance measures continue to be challenging, and precise prevalence of SCD has not been determined (Centers for Disease Control & Prevention [CDC], 2012a; 2012b). Current estimates are that 70,000 - 100,000 persons are affected in the U.S., and millions of persons are affected globally (USDHHS, 2014). In the U.S., stakeholders include persons with SCD, approximately 2-3 million people living with sickle cell trait (SCT), family members, communities of interest (local, regional, and national sickle cell organizations), employers, health care providers, researchers, insurers, and government agencies (USDHHS, 2011; USDHHS, 2014). This dissertation compendium explores three components examining factors of one topical area affecting the lives of persons with sickle cell disease (SCD): (a) Integrative Review of Pain Instruments, (b) The Application of Genomic Testing for Pain Management, and (c) Associations of Psychosocial Measures with Quality of Life in a Sample of Adults with Sickle Cell Disease (Table 1).

Background

In persons unaffected by SCD, erythrocytes (red blood cells [RBCs]) are highly flexible biconcave disc-shaped cells that make up 42-45% of blood volume. Each normal RBC has a 120-day life cycle. Blood contains around 5 million RBCs per cubic millimeter. Each RBC consists of 200-300 million molecules of hemoglobin. Hemoglobin (Hb) transports oxygen and carbon

dioxide throughout tissues and facilitates the maintenance of blood pH balance (Patton & Thibodeau, 2013).

In persons affected by SCD, RBCs sickle as a result of a single mutation of the hemoglobin beta gene (HbB) located in the short arm of chromosome 11 at position 15.5. HbB provides the genetic code for the protein beta globin, which makes up 2 of the 4 subunits of hemoglobin (NLM, 2015a). In one SCD mutation, glutamic acid is replaced with valine, changing the beta globin subunit and creating significant consequences. This mutation produces abnormalities of the hemoglobin's molecular structure that result in rigidly sickled cells, an erosion of the cells' functional attributes, and a disruption in their normal longevity from 120 days to about 20 days. These sickled cells have a tendency to adhere to the vascular endothelial membrane, causing painful vaso-occlusive episodes (VOEs), tissue ischemia, inflammation, and organ damage (Ballas, et al., 2010; Bender & Douthitt Seibel, 2014; Northen, 2008). This cascade of pleiotropic and biological events triggers potentially fatal physiological pathologies affecting the psychological and social dimensions of persons with SCD (Ballas et al., 2010; Engel, 1977; Thomas, Stephenson, Swanson, Jesse, & Brown, 2013).

Mortality Factors

In 1973, the median age of death in persons with SCD was just over 14 years according to a seminal study based on autopsies (Diggs, 1973). In the following 2 decades, survival rates increased to 20 years (Platt et al., 1994). Neonatal testing, improvements in health education, and preventive measures have resulted in fewer early deaths and longer average life spans in persons with SCD (Telfair, Alexander, Loosier, Alleman-Velez & Simmons, 2004). Preventive measures include vaccinations, antibiotic in the first 5 years of life, the use of Hydroxyurea to increase fetal hemoglobin, and transcranial Doppler and packed red blood cell transfusions as stroke

management strategies (Hankins et al., 2014; Hussain, Nichols, Bowman, Xu, & Neunert, 2015; Ware et al., 2011). A more recent study examining 16,654 sickle cell deaths from 1979-2005 reported that the median age at death was 42 years for women and 38 years for men (Lanzkron, Carroll, & Haywood, 2013).

Due to the median age increase, adults with SCD require new strategies to improve their health outcomes and promote quality of life throughout their lifespan. Health management strategies therefore should encompass pain control and health-related factors.

Morbidity Factors

Pain. Pain is the hallmark symptom of SCD, and coordinated care planning for pain management is of primary importance (United States Department of Health [USDH], 2002; USDHHS, 2014). The health care needs of persons with SCD vary throughout their lives. Patients with SCD experience both chronic and acute pain (Ballas et al., 2010; Taylor, Stotts, Humphreys, Treadwell, & Miaskowski, 2013). In early adulthood, individuals with SCD experience increased incidences of acute pain resulting in hospitalization for VOEs or pain crises (Jenerette & Brewer, 2010; Serjeant, 1997), increased physical disability, and difficulty maintaining or getting employment due to frequent hospitalizations.

System-related factors. SCD can affect every organ system (Ballas et al., 2010). In addition to VOEs, adults with SCD may experience acute renal failure (ARF), priapism, hepatobiliary complications, acute and chronic anemia, splenic sequestration, acute chest syndrome (ACS), avascular necrosis, pulmonary hypertension, and many other complications (USDHHS, 2014).

Neurocognitive factors. As individuals with SCD mature, they have an increased risk of age-related cognitive decline (Vichinsky et al., 2010). Age-related decline, chronic anemia, and

ischemic or hemorrhagic events associated with SCD may play a significant role in neurocognitive impairment.

Psychosocial factors. Disease burden, frustrations, and stigma increase the likelihood of psychosocial problems including depression (Edwards et al., 2009; Jenerette & Brewer, 2010; Jenerette, Funk, & Murdaugh, 2005). Depression in persons with SCD often goes unidentified and unmanaged (USDH, 2002). Poor communication and patient stigmatization have resulted in perceived maltreatment and lack of trust in the provider-patient relationship (Jenerette & Brewer, 2010; Haywood et al., 2010) and may factor into psychosocial concerns affecting patient stress, self-esteem, and hopelessness. The complexity of this disease with its biological (pain), genetic, and psychosocial components requires holistic management that is tailored to the individual.

Problem Statement

Biological, psychological, social, religious/spiritual, and genetic health determinants contribute significantly to quality of life for persons with SCD. Evaluating the positive and negative impact of these determinants affords researchers opportunities to identify and design interventions to improve health outcomes in persons with SCD (Braverman, Egerter & Mockenhaupt, 2011; Marmot & Wilkinson, 2011).

Gaps in Literature

As discussed in detail in the integrative review (Chapter 2 of this compendium), much prior research has addressed pain in persons with SCD; however, research is scarce on pain instruments that include religiosity and spirituality measures (Adegbola et al., 2011; Cooper-Effa et al., 2001; Taylor, Stotts, Humphreys, Treadwell, & Miaskowski, 2013). In the study by Adegbola et al. persons with SCD reported that numeric pain scales were inadequate at communicating pain needs; participants also reported that faith helped them to manage pain and

hoped for an assessment that was comprehensive in conveying their pain experience (2012). Thus, inclusion of biopsychosocial-religiosity/spirituality dimensions to instruments used to measure the pain of persons with SCD may provide greater knowledge of the pain experience.

As discussed in the accompanying literature review (Chapter 3 of the compendium), few studies have explored the utilization of genetic testing of persons with SCD to prescribe medications. Genetic testing may result in the selection of pain-relieving agents that are safer, more efficacious, and individually tailored for a lifetime of chronic and acute pain management.

The secondary analysis (Chapter 4 of the compendium), examined data to identify whether the quality of life of respondents with SCD was statistically significantly associated with psychosocial health, specifically depressive symptoms, coping, social support, and self-efficacy. Such findings could be foundational and guide future research directed in the development of evidence-based psychosocial guidelines.

Design and Method

The first manuscript, an integrative review, analyzed quantitative studies of pain instruments using a biopsychosocial (BPS) framework in accordance with the National Pain Strategy (USDHHS, 2015). The analysis examined religiosity and spirituality (R/S) measures to determine whether the inclusion of R/S to existing or new pain instruments might be an appropriate additional measure to improve cultural competence, comprehensive care, and self-care management for persons with SCD. The second manuscript, a literature review, explored the current science of personalized or precision medicine for sickle cell patients with refractory pain during vaso-occlusive episodes (VOEs) to determine if those patients might benefit from genetic/genomic testing. The review reiterated the importance of nurses having a working knowledge of genomics and pharmacogenomics to support safer practice and to enhance patient

and family teaching and advocacy through the use of genetic testing that can assist providers in personalizing treatment for patients with sickle cell disease. The final manuscript, a secondary analysis of data from 179 study participants with SCD from two southeastern U.S. clinics, examined associations among quality of life, depressive symptoms, self-efficacy, social support, and coping. Linear regression analyses were used to examine the associations among the variables. By evaluating the associations among the psychosocial dimensions in this compendium, the secondary analysis lays the groundwork for future studies to explore best practices for humanistic SCD care, thus helping to address a significant research gap. Currently, no evidence-based practice guidelines exist for psychosocial health needs in persons with SCD, although studies have suggested that the psychiatric mental health needs of this population are greater than the national average.

Theoretical Frameworks

Each manuscript has a distinct theoretical framework. Engel's (1977) biopsychosocial (BPS) model of patient care provides for the conceptualization of a full range of human experience in health and disease in the integrative review. This model integrates biological, psychological, and social dimensions. Additionally, informed by the findings, the investigator recommended religiosity and spirituality assessments be included to assess the pain experience of persons with SCD more holistically. In the literature review, the author used Rogers's Diffusion of Innovation model to posit that when stakeholders communicate consensus about an innovation, adoption of the innovation will likely occur, particularly when additional support for the innovation exists within the organization (Horner, Abel, Taylor, & Sands, 2015; Rogers, 2003). The Rogers model is important because it has a record of success in improving interpersonal communications among stakeholders, often resulting in the adoption of practice

change. The Self-Care Management for Sickle Cell Disease (SCMSCD) model (Jenerette, 2004; Jenerette & Murdaugh, 2008) was the theoretical framework of Jenerette's original dissertation research study. In the secondary data analysis, the SCMSCD model was valuable for the examination of associations among vulnerability factors, self-care management resources, and health outcomes.

The combination of validated existing pain scales with validated measures of religiosity, spirituality, and psychosocial factors can guide future research to assess persons with SCD holistically. Although personalized (or precision) medicine that uses genetic testing is in its infancy, patients and providers are using genetic testing to ensure safe and specific therapies. The SCMSCD model can be used to guide nursing interventions for this vulnerable population.

Grounded in the latest understanding of interdisciplinary team care for patients and families, this compendium of studies relies upon holistic concepts and available scientific and humanistic understanding to address the multidimensional needs of persons with SCD. Until genetic interventions are introduced that correct the genetic code mutation responsible for triggering the sickling of RBCs, (Chandrakasan & Malik, 2014; Hoban et al., 2015; Perumbeti & Malik, 2010; Romero, 2013) holistic health management is a worthy recourse to address pain and disease-related complications in this patient population (Koshy & Dorn, 1996; Smy, 2004; Thomas et al., 2013).

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Table 1. Manuscript Comparisons

	Manuscript 1	Manuscript 2	Manuscript 3
Title	<i>Integrative Review of Pain Instruments for Sickle Cell Patients in the Emergency Setting</i>	<i>The Application of Genomic Testing for Pain Management in Sickle Cell Disease</i>	<i>Associations between Psychosocial Measures in a Sample of Adults with Sickle Cell Disease</i>
Topics	Pain measures biopsychosocial	Genomic testing	QoL, depression, psychosocial influences
Method	Integrative review	Literature review	Secondary data analysis
Population issues	Persons with sickle cell holistic pain management	Persons with sickle cell holistic pain management	Persons with sickle cell holistic health management; QoL*depression
Instruments	Patient assessment tools re: pain	Patient assessment tools re: genomics	Patient assessment tools re: psychosocial attributes
Findings	Recommendations for practice and evaluate patient outcomes	Recommendations for practice and evaluate patient outcomes	Recommendations for practice and evaluate patient outcomes
Innovation	Proposing the addition of Religiosity/Spirituality dimensions to existing pain instruments	Proposing the addition of Genomic testing, emphasizing the concepts of precision/ personalized healthcare	Proposing the expansion of EB practice guidelines to include psychosocial dimensions
Future work based on findings	Develop and use pain instrument; measure persons with SCD using a pain instrument with Biopsychosocial – religiosity/sprituality components in the ED during VOC	Advocate for genetic testing of patients with SCD. Utilization of DOI to facilitate interpersonal communications among stakeholders, evaluate the adoption of practice change and then measure the health outcomes associated with providers adopting genetic testing for prescriptive decision-making.	Collect evidence needed to substantiate the inclusion of EB practice guidelines that support the psychosocial needs of patients with SCD
Recurrent Theme(s)	Support literature identifies: pain hallmark of SCD; disparity, stigma	Support literature identifies: pain hallmark of SCD; disparity, stigma	Support literature identifies: pain*SCD; disparity, stigma Lack of support for psychosocial health needs
Theoretical Model	Biopsychosocial	Diffusion of innovation (DOI)	Self-care management of SCD

QoL= quality of life; EB = evidence-based; SCD= sickle cell disease; ED= emergency department; VOC/E= vaso-occlusive crisis/episode

Chapter 2

Integrative Review of Pain Instruments for Sickle Cell Patients in the Emergency Setting

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Abstract

Objectives: This integrative review analyzes pain instruments using a biopsychosocial (BPS) framework in accordance with the National Pain Strategy. Religiosity and spirituality (R/S) measures were analyzed to assess whether the instruments include R/S and how this aligns with the BPS framework. An instrument inclusive of BPS-R/S measures may contribute to comprehensive pain assessment for persons with sickle cell disease (SCD).

Methods: A review of the literature was conducted following a search in ProQuest Nursing and Allied Health Source, National Library of Medicine (PubMed), Cumulative Index for Nursing and Allied Health Literature (CINAHL), and PsycINFO. The BPS model modified with R/S dimensions provided the framework to evaluate pain instruments that can be used to measure pain in persons with SCD in emergency departments (ED). Inclusion criteria were unidimensional and multidimensional pain instruments, as well as scholarly peer-reviewed quantitative studies of human subjects published in English between 2003 and 2013.

Results: Ten instruments were examined for their biometrics and biological, psychological, social, religious, and spiritual (BPS-R/S) dimensions. The Wong-Baker Faces Scale (unidimensional) and the PAINReportIt (multidimensional) instruments demonstrated the strongest validity for use with persons with SCD in the ED during acute pain crises. None of the ten instruments included the dimensions of religiosity and spirituality.

Conclusion: The use of pain instruments containing BPS components may facilitate meaningful treatment planning. The use of multidimensional instruments with the addition of R/S instruments is in accord with self-care strategies used by persons with SCD.

Keywords: Pain, sickle cell, measurement, instruments, validity, biopsychosocial, religiosity, and spirituality.

Integrative Review of Pain Instruments for Sickle Cell Patients in the Emergency Setting

Pain is the hallmark symptom of patients with sickle cell disease (SCD) (Ballas et al, 2010; Jenerette & Brewer, 2010; U.S. Department of Health and Human Services [USDHHS], 2014). Rapid assessment and initiation of parenteral opioid therapy is a necessity for the management of pain associated with vaso-occlusive crisis (VOC) in the emergency department (ED) (Ender et al., 2014). Pain control for the patient with sickle cell has been reported to be inadequate in the ED resulting in patient dissatisfaction, return ED visits, hospitalizations, and fatalities (Ender et al., 2014; Solomon, 2010).

The purpose of this review is to investigate pain instruments that can be used in ED settings for persons with SCD during vaso-occlusive crises (VOC). The biopsychosocial (BPS) framework recommended by the National Pain Strategy guided the evaluative process. In addition to the biological, psychological, and social, dimensions, religiosity and spirituality (R/S) dimensions were included in order to determine the existence and efficacy of comprehensive pain instrument(s).

Background

Sickle cell disease (SCD) is a recessive, genetic, hematologic disorder affecting 70,000 - 100,000 Americans (USDHHS, 2014). Several sickle cell genotypes result in variations in disease characteristics. Persons with homozygous hemoglobin SS (Hb SS) and hemoglobin S β thalassemia (Hb S β) genotypes and those with lower levels of fetal hemoglobin (HbF) experience severe complications. The etiology of SCD and abnormal 'sickle'-shaped red blood cells (RBC) is due to the amino acid substitution of glutamic acid by valine, located in the beta globin subunit of hemoglobin at the 6th amino acid position (Ghatpande, Choudhary, Quinn, & Goodman, 2008).

Individuals with SCD experience various complications including vaso-occlusive crises (VOC), also known as vaso-occlusive episodes (VOE) or sickle cell crises (SCC) (Frei-Jones, Baxter, Rogers, & Buchanan, 2008). During VOC, misshaped and inflexible RBCs obstruct the flow of oxygenated blood to cells, tissues, and organs resulting in inflammation, tissue damage, and excruciating pain (Centers for Disease Control and Prevention (CDC), 2011; Smith & Scherer, 2010; U.S. Department of Health and Human Services (USDHHS), 2011a; U.S. Department of Health and Human Services (USDHHS), 2014). It is difficult to assess the physiologic impact of VOC and the accompanying pain. Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey, 1994, p.569). Pain also has been described as “whatever the experiencing person says it is, existing whenever the experiencing person says it does” (McCaffery, 1968, p.95).

Pain measurement and control are priority elements of care for the person in VOC. For the purposes of this paper, pain measurement is either the use of unidimensional instruments to assess pain intensity, generally using a self-reported rating scale, or the use of multidimensional instruments to rate pain intensity, describe pain location, quality, duration, and pattern, and in some instances, evaluate the patient’s behavioral coping strategies for pain.

This integrative review is an analysis of the scientific literature reporting reliability, validity, and feasibility of instruments used to measure the pain experience of persons with sickle cell disease. It contains information pertaining to the state of the science, identifies theoretical concepts, and recommends instruments useful for clinical practice in the emergency department (ED) setting (Whittemore & Knafl, 2005). A biological, psychological, social, religious, and

spiritual (BPS-R/S) theoretical approach was used to evaluate whether current pain instruments are useful for patients with SCD as well as to recommend future research.

Pain management associated with VOC and several other serious complications requires emergency treatment (Tanabe et al., 2010), which includes management of pain, dehydration, infection, and other acute issues. Treatment includes, but is not limited to, opioid agents (Dampier et al., 2013). Despite established treatment regimens and algorithms, patients with SCD report experiencing inadequate pain control and care during VOC in their emergency experiences (Dorsey, Phillips, & Williams, 2001; Lattimer et al., 2010). The pain associated with a VOC can last from hours to weeks (Human Genome, 2005), and these ischemic episodes have resulted in disability and death (Ghatpande et al., 2008). The frequency of VOC varies, and a range of pathophysiologic phenomena may occur throughout the lifespan of persons with SCD (Lettre et al., 2008; Tanabe et al., 2010). Some patients may experience as few as one crisis per year, and some may have as many as 25 (Jenerette, 2004); however, Brousseau and colleagues defined 3 or more hospitalizations for VOC in a 3-year period as severe disease (Brousseau, McCarver, Drendel, Divakaran, & Panepinto, 2007).

Nurses have an integral role in conducting best practices associated with ED care and pain management during patient assessment, education, medication administration, and in determining the efficacy of doses administered. Nursing leadership and advocacy in the ED management of the patient with SCD is crucial in promoting culturally competent care and facilitating positive health outcomes, especially related to assessment and control of pain (Wilson & Nelson, 2015). This review (a) explores multiple pain scales used to evaluate acute and chronic pain and (b) identifies instruments used in studies to measure pain in patients with

SCD, and (c) assesses the biometrics and the biological, psychological, social, religious, and spiritual (BPS-R/S) dimensions of those pain scales.

Theoretical Framework

(Borrell-Carrió, Suchman, & Epstein, 2004; Engel, 1980; Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Roth, Geisser, & Williams, 2012; Smith et al., 2005). The biopsychosocial model is highly referenced by the National Pain Strategy (NPS) and others as a means of assessing, planning, implementing, and evaluating pain care in a manner that is specific to the needs of the person in pain (USDDHS, 2015). Taylor, Stotts, Humphreys, Treadwell, and Miaskowski (2013) recognized the significance of integrating religiosity and spirituality into the BPS model. Research that measures these additional areas and their associations with pain and pain control may be useful in developing pain management strategies. Taylor et al. and other researchers have validated using a more holistic perspective to enhance provider/researcher understanding beyond the disease concept, into the additional areas of life control, social support, coping, self-management, and transcending disease (Adegbola, 2011; Cooper-Effa, Blount, Kaslow, Rothenberg & Eckman, 2001; Cotton et al., 2009; Harrison et al., 2005; Tanyi, 2002; & Yoon & Black, 2006).

This review evaluates the evidence of instruments using the BPS framework integrated with the concepts of religiosity/spirituality (Table 1). Religiosity/Spirituality will be connoted as 'R/S' for the remainder of this manuscript. Religiosity embodies belief in a higher power or God and may include participating in organized spiritual practices such as prayer groups or church attendance (Tanyi, 2002). Spirituality will be conceptually defined as a personal experience that is beyond the corporeal, It has been described as a "synthesis of personal beliefs about the essence of being" (Adegbola, 2011) that "involves humans' search for meaning in life...

acceptance of hardship and mortality, a heightened sense of physical and emotional well-being, and the ability to transcend beyond the infirmities of existence” (Tanyi, 2002). Spirituality is operationally defined as any instrument containing items pertaining to faith or beliefs, the value or importance of faith or beliefs, the use of faith or beliefs as a means of coping with biological, psychological or social stressors, identifying participation in a community of faith or responses to action steps in support of faith or beliefs (Draper, 2012). Although specific definitions of religiosity/spirituality (R/S) differ, there are similarities in patient/participant interpretation of these terms. In one sample of adolescents, 11-19 years of age, 46% believed that R/S meant the same thing, (Cotton et al., 2009).

While there has been significant debate about spiritual care in the public healthcare environment (Draper, 2012), academic and theoretical debates have little to do with the actual beliefs of patients and research participants. General screenings of persons with SCD to determine their religious and spiritual status are valuable from the natural systems perspective and are inclusive of patients’ needs (Draper, 2012; Engel, 1977). The current study is grounded in the belief that using a BPS-R/S theoretical approach will result in improvements to comprehensive and culturally competent pain management because prior studies of participants with SCD have identified that religiosity and spirituality are important to them (Adegbola, 2011; Cotton et al., 2009; Harrison et al., 2005; Jenerette & Lauderdale, 2008; Taylor, Stotts, Humphreys, Treadwell, & Miaskowski, 2013).

Methods

Literature Search Methods: Following consultation with a research librarian, a search of quantitative literature was conducted for instruments measuring pain in individuals with SCD in the following databases: ProQuest Nursing and Allied Health Source, National Library of

Medicine (PubMed), the Cumulative Index for Nursing and Allied Health Literature (CINAHL), and PsycInfo. The following terms were used in ProQuest: “pain,” “sickle cell,” and “instruments.” The search yielded 346 articles. Limiters included quantitative, scholarly, peer-reviewed, human subjects, all age groups, document types identified as evidence-based healthcare, and literature reviews in the English language written between 2003 and 2013. One-hundred and three studies remained and were hand sorted for specific instruments used to measure pain in patients with SCD, with preference for patient status of VOC. Four studies met the inclusion criteria after reviewing and sorting the ProQuest database search.

In the initial PubMed search, the key terms “pain,” “sickle cell,” and “instruments” yielded four studies. Upon review, the first two were excluded for being out of the selected period (one was published in 1993 and another in 1996), and the third and fourth studies were excluded for not addressing pain specific instruments used in the SCD population. A second search of PubMed using “pain,” “sickle cell,” and “validity” resulted in 19 studies. After a review of the abstracts and other subsections, 3 studies were retained because they met the criteria and also provided information about the validity of pain scale instruments.

In the CINAHL database, no studies were found using the key terms “pain,” “sickle cell,” and “validity”; “pain,” “sickle cell,” and “measurement”; or “pain,” “sickle cell,” and “instruments.” A broadened search using the terms “pain” and “sickle cell” resulted in 254 articles. Limits were set to include the previously mentioned time frame, the source type from academic journals, either gender, all ages, and the subheadings pain and emergency care. After studies outside the U.S. were excluded, twelve articles remained. A hand search involving the review of abstracts, methods, samples, and results led to the retention of 3 studies.

A PsycINFO search using the thesaurus key words “Test Validity,” “Sickle Cell,” and “Pain” yielded four results; of these, two were qualitative, one was a duplicate previously identified through a search in ProQuest, and one did not meet the inclusion criteria. No additional studies were retained from PsycINFO. See Figure 1 for an overview of search methods.

Methods for Assessment of Instruments: The investigators evaluated the validity, reliability, and feasibility of pain instruments from ten SCD studies. The Oxford Centre for Evidence Based Medicine (OCEBM) guidelines were used to evaluate and rank the evidence in the studies using a Likert-like scale of 1-5; the smaller number indicates higher level study evidence (Howick et al., 2011).

The studies were examined for theoretical approach, and the instruments were examined for associations with BPS-R/S dimensions (Dampier et al., 2013; Edwards, et al., 2006; Frei-Jones et al., 2008; Luffy & Grove, 2003; McClellan et al., 2009; Myrvik et al., 2013; Smith et al., 2005; Wilkie et al., 2010; Zempsky et al., 2013a & Zempsky et al., 2013b). The BPS dimensions were operationalized as a pain instrument measuring the biological, psychological, and social attributes of pain including intensity levels, descriptive assessment of patient burden, affective of emotional measures, adaptation and functional status (Benjamin, 2008).

Results

The authors identified that the 10 studies all contained higher-level evidence with a rating of 2 on the 5-point scale. Ten pain instruments were evaluated within the 10 studies included in this review and are listed in Table 1.

Of the 10 pain instruments used with patients with SCD, the most frequently used instrument was the visual analog scale (VAS) (Dampier et al, 2013; Edwards, et al., 2006; Luffy & Grove, 2003; McClellan et al., 2009 & Myrvik et al., 2013). The Wong-Baker Faces Scale

(WBFS) was the preferred unidimensional instrument for African American preschool-aged and older children with SCD (Luffy & Grove, 2003; McClellan et al., 2009).

Table 1 also lists the instruments by unidimensional and multidimensional status. Four studies used 1 or more unidimensional instruments (Frei-Jones, et al., 2008; Luffy & Grove, 2003; Myrvik et al., 2013; Zempsky et al., 2013b), and 5 studies used unidimensional in conjunction with multidimensional instruments (Dampier et al, 2013; Edwards, et al., 2006; McClellan et al., 2009; Smith et al., 2005; Wilkie et al., 2010).

Of the 10 studies reviewed, only two described using a theoretical framework. Luffy & Grove (2003) used Leininger's Theory of Nursing Cultural Care Diversity and Universality to communicate the importance of using instruments that are valid, reliable, and culturally competent when examining non-white children during sickle cell clinic visits. Smith et al. (2005) used a combination of research models: Andersen's health care utilization, Engle's biopsychosocial (BPS) theory, and the Health Belief Model (HBM) to develop a conceptual framework of pain and response to pain in SCD. Their multidimensional approach using diary entries solicited descriptive reflections of coping strategies; this exercise resulted in a need for less health care support. The design of the diary contains very useful inquiries for health reflection, but not for the emergent needs of persons in acute pain. Table 1 lists the dimensions of the BPS in each of the instruments. None of the pain instruments addressed religiosity/spirituality.

As indicated in Table 1, all of the multidimensional instruments evaluated the biological and psychological dimensions, and some included social influences of the patient's pain experience (Dampier et al, 2013; Edwards, et al., 2006; McClellan et al., 2009; Smith et al., 2005; Wilkie et al., 2010; Zempsky et al., 2013a).

The VAS has a demonstrated record of success (Salo et al., 2003), and the WBFS was preferred by youths. For each unidimensional instrument, key factors regarding their clinical use include: the respondent must understand the instrument being administered, consistent use by knowledgeable providers is essential (Berry et al., 2001; Herr & Garand, 2001), and the provider needs to be responsive to the intensity rating stated by the patient (Schiavenato & Alvarez, 2013).

The multidimensional instruments used in the clinical studies assessed in this review can guide the development of interventional strategies associated with the pain experience. Each of the instruments has components that provide a greater understanding of pain burden and experience.

Samples

Two studies evaluated the adult (18 years or older) population (Edwards et al., 2006; Wilkie et al., 2010), and the remainder were a mix of ages primarily consisting of children and young adults 2-21 (Table 2).

The samples in the studies identified the racial and ethnic backgrounds of those with SCD as African American/Blacks: 76% - 93.8%, Caucasian/Whites: 1.4% - 8%, Hispanics: 2.8% - 12%, and those who identified as being of more than 1 race: 2.1% - 12% (CDC, 2011; Wilkie et al., 2010; Zempsky et al., 2013a & Zempsky et al., 2013b). Some of the studies did not identify the racial demographic of the participants (Dampier et al., 2013; Edwards, et al., 2006; Frei-Jones, et al., 2008; McClellan et al., 2009; Myrvik et al., 2013; Smith et al., 2005).

There were no exclusions based upon sickle cell genotype in the selected studies. Six studies had no age exclusion (Dampier et al., 2013; Frei-Jones et al., 2008; Luffy & Grove, 2003; Myrvik et al., 2013; Smith et al., 2005; Zempsky et al., 2013b).

Reliability and Validity

In many studies, the pain instruments were well established and reports of their reliability and validity were based upon prior research. Standard reliability analyses were reported in 6 of the 10 studies using Pearson's r scores, Cronbach's alpha, test-retest, or inter-rater procedures. Validity analyses were reported in 7 of the 10 studies. Content, convergent, construct, and concurrent validities were identified. Reliability and validity in the unidimensional instruments were $r = 0.54 - 0.72$ p -value $<.001$ and content validity per Kendall's coefficients 0.726 , $p < 0.01$ for the African American Oucher Scale (AAOS); $r = 0.63 - 0.94$, $p < 0.001$ and concurrent validity = $\chi^2 = 1.21$, $df = 5$ for the WBFS; $r = 0.87$ and construct validity $r = 0.44$, $r = 0.28$, $r = 0.44$, $p < 0.001$ between parent and child, nurse and child, nurse and parent for the VAS (Luffy & Grove, 2003). No reliability or validity data were given for the numeric rating scale (NRS) however, Zempsky et al., reported established validity in other cited work (2013) (Table 2). Reliability and validity statistics in the multidimensional instruments were not reported in Dampier et al. for the Brief Pain Inventory (BPI). The daily pain diary study did not have reliability and validity data; however, face validity was discussed and Gil, Carson, & Sedway, 2000, reported that pain diaries have been used with success in this population (Smith et al., 2005). McClellan et al. reported criterion validity $r = 0.49$ $p < 0.01$ and a reliability range of $0.68 - 0.72$ for the observable scale of behavioral distress (mOBSD). Wilkie et al., referenced validity found in another study (Jha et al., 2010) in a sample of persons with sickle cell and a 30-year research use to establish validity and Cronbach's alpha for internal consistency reliability of $.63$, $.77$, and $.75$ in the barrier portion of the computerized McGill Pain Questionnaire entitled *PAINReportIt* (2010). Zempsky et al, 2013a reported construct validity between group $t = -5.12$, $p < 0.001$ and reliability using Pearson correlation coefficient $r = .08$, $p < 0.001$ (Table 2).

Feasibility

The time required to administer an instrument is significant when assessing patients in sickle cell crisis. Many of the unidimensional scales and the pain intensity sections of the multidimensional scales (VAS, AAOS, NRS, and WBFS) contain self-report tools that require minimal time and minimal or no cost, with low participant burden (Table 2). Unidimensional instruments are highly regarded for their efficient assessment of acute pain intensity at the time of a VOC. The time required to complete a unidimensional instrument was typically 1 minute.

Discussion

The purpose of the review and the theoretical framework served as the guidelines for instrument selection. When choosing a unidimensional instrument to measure pain rating in the clinical setting, providers must consider the age of the person being evaluated. In selecting the best unidimensional instrument, reliability, validity and feasibility should be considered in addition to the preferences of the sample (Luffy & Grove, 2003).

Although the studies had reliability, validity, and feasibility, the decade in which they were published was characterized by patients reporting their pain needs were not met, and providers reporting frustration in their caregiver role with persons with SCD (Lattimer et al, 2010; Mathias & McCavitt, 2015; Tanabe et al., 2010). Many studies of persons with SCD report stigmatization and disparate care (Haywood et al., 2009; Haywood et al., 2014; Jenerette, 2004; Jenerette & Brewer, 2010; Jenerette, Funk, & Murdaugh, 2005). Addressing the issue of stigmatization among all providers and suboptimal care in the ED (Schiavenato & Alvarez, 2013) is pivotal to making the changes needed to improve pain care in the ED setting. Nurses are essential in managing the existing patients' perceptions of stigma through the utilization of

patient advocacy, clinical expertise, and the nursing process in pain management (Wilson & Nelson, 2015).

Unidimensional scales are brief, thus useful in the ED, but they have limitations; they are self-report instruments and offer information pertaining to pain intensity only. Research has identified that providers underrate self-reported data and question the value of unidimensional instruments in measuring the extreme pain of VOC (Schiavenato & Alvarez, 2013). On these scales, a rating of 0 means the pain is absent; 5 or 10, depending on the scale, indicates pain is at its worst (Luffy & Grove, 2003), yet perceptions of pain intensity can vary greatly among patient populations. The visual analog scale (VAS) a unidimensional instrument, is well established in the population with sickle cell, but has poorer efficacy in young children (Luffy & Grove, 2003) as well as persons with learning deficits or cognitive impairment (Berry et al., 2001; Herr & Garand, 2001).

While multidimensional instruments are meritorious, respondent burden must be considered when administering instruments from this group in the ED environment. Multidimensional instruments contain specific items used to obtain information pertaining to the multiple characteristics of the patients' pain. These instruments allow more details of the unique features of the patients' pain experience (Dampier et al., 2013; Wilkie et al., 2011; Zempsky et al., 2013a). Time to completion and respondent burden during an acute pain episode are the main limitations. The SCPBI-Y, a multidimensional instrument, has a 1-minute completion time but it lacks necessary ED screening information, such as a pain scale, since it measures pain burden.

Evidence-based strategies used with a BPS-R/S approach may contribute to the assessment of persons with SCD by including additional holistic dimensions that patients may

appreciate. Research demonstrates that many persons with SCD value spirituality and religiosity (Adegbola, 2011). Research that creates R/S assessment items or uses existing instruments that measure these concepts also can be designed to address the cultural and traditional values of some persons with SCD and, thus, may result in a more culturally competent and comprehensive assessment. This information will enhance provider and researcher knowledge and should be considered for assessment and for care planning (Taylor et al., 2013). Provider support of spirituality and religiosity practices is linked to patient perceptions of decreasing (or decreased) pain, the hallmark symptom of SCD (Cooper-Effa et al., 2001; Taylor et al., 2013).

Several instruments have been used in healthcare research to measure spirituality. Adegbola (2011) and Cotton et al. (2009) used the Functional Assessment of Chronic Illness Therapy-Spiritual (FACIT-Sp), a 12-item instrument to measure spirituality in persons with SCD. Draper identified nine “General Spirituality” and seven “Spiritual Wellbeing” instruments in an integrative review of spiritual assessment (2012, p.973). For organizations introducing spiritual assessment to their clinical environment, the researcher suggested the Faith and Belief, Importance, Community, Address in Care or Action (FICA) model. FICA is a 4-step model that is considered general because it is not specific to a particular religious or spiritual group, and it is easy to administer (Draper, 2012).

Asking participants to identify their ethnic and racial identities is valuable because this cannot be assumed by appearance. Health officials are attempting to gather accurate demographic information about persons with SCD (CDC, 2014; Taylor et al., 2013). While the majority of persons with SCD in the United States are African American (Black), SCD is present in other racial and ethnic minority groups. These groups include people who are Mediterranean,

Arabian, Indian (East), South American, Central American and Caribbean or their descendants (Piel et al., 2010; USDHHS, 2011b).

Herr & Garand identified age, culture, ethnicity, gender, spiritual and family as influential factors to consider when assessing pain (2001). It is also essential to evaluate the mental status and for other barriers to understanding. Using an interdisciplinary approach to pain management may be helpful in addressing the factors that impede understanding and successful outcomes.

Younger participants and those experiencing communication barriers typically have had difficulty with the linear unidimensional scales (VAS and NRS) and have fared better with faces scales, e.g. the AAOS and WBFS scales (Luffy & Grove, 2003; Flaherty, 2012). However, facial expressions are culturally determined, and limits exist regarding the universality of the faces instrument. Children have preferred the WBFS. Yet the WBFS can be used to assess persons of any age unless the individual is visually or cognitively impaired. The faces scale also contains a 0 - 5 numeric rating under each pictured face.

When choosing a multidimensional instrument, the following factors are significant: the reliability, validity, ED feasibility, BPS framework, the age of the participant, and successful use in persons with SCD. The mean ED wait time is 46.5 minutes to 58.1 minutes (Hing & Bhuiya, 2012). This timeframe provides an adequate opportunity for the administration of most multidimensional instruments. The *PAINReportIt* instrument was consistent with the aforementioned criteria for use in the ED during acute pain crises because it has a history of success in research with persons with SCD, it addresses 2 (biological and psychological) of the 5 pain dimensions (BPS-R/S), and it includes integral findings (pain location, rating, and

biological and psychological factors) needed to manage acute pain in the ED (Wilkie et al., 2010).

Based on this in-depth review of the research on the 10 identified instruments, the investigators determined that the *PAINReportIt*, a multidimensional instrument, has an average completion time of 21.4 minutes, making it viable for ED use. Descriptive analysis, Pearson's correlations, and Students *t* tests were used to examine the associations among the variables. Cronbach's α for internal consistency reliability ranged from .63 - .77 in the Barrier Questionnaire component of the instrument. Correlations among pain rating indices (PRI) were in unison with similar studies and contributed to the validity of the Wilkie et al. study (2010). The first McGill Pain Questionnaire (MPQ) was published in 1975 (Melzack, 1983) and has a 30-40-year history of being used to measure pain. The *PAINReportIt* software is a computerized version of the MPQ, a multidimensional instrument developed by Nursing Consult LLC. Researchers followed a structured protocol in the delivery of the pain assessment instrument and were available to respondents for questions (Wilkie et al., 2010). This instrument does not contain R/S components. An additional instrument with R/S variables may provide an opportunity for testing the utility of R/S factors.

Limitations

The results of the search of quantitative literature for instruments measuring pain in individuals with SCD during VOC were limited. The 10 pain instruments evaluated the pain of patients with SCD during VOC and non-VOC events. The search was also limited to studies produced in the United States.

Implications

Patients typically expect comprehensive assessment of their current health status, clear communication, and prompt pain management (Lattimer et al., 2010). Providers and researchers value instruments that facilitate detailed and systematic guidance of the health care needs of persons with SCD. The acute pain in VOC is not merely a physiological phenomenon; it is associated with chronic disease progression, as well as biopsychosocial and spiritual factors. Utilizing multidimensional instruments broadens researcher and provider knowledge about the quantitative and qualitative indices of the pain experience of patients with SCD.

The pain experience is difficult to assess because pain is unique to the person. As a basis for developing optimal planning in the care environment, it is necessary to determine the validity, reliability, and feasibility of instruments used to measure pain. The use of well-established and comprehensive instruments to measure patient needs and to establish an algorithm for pain management to decrease pain and tissue damage during VOC will improve provider effectiveness and decision-making with patients and, thus, optimize health management (Adegbola et al., 2012; Tanabe et al., 2010; USDHHS, 2014). The results from this review can help provide a foundation to assess and develop interventions associated with a natural systems approach to illness management, including research on new protocols for persons with sickle cell disease (SCD). Testing the use of the *PAINReportIt* instrument and FICA 4-step model may provide data useful in improving outcomes in persons with SCD.

Conclusion

The agendas of the National Pain Strategy (NPS) validate the importance of the biopsychosocial (BPS) approach to pain care with numerous references to the model (USDHHS, 2015). The addition of the religious and spiritual dimensions to the framework extends the

model and serves as the foundation and guide for this review. Using a BPS-R/S approach encourages primary providers to engage in interdisciplinary collaboration with psychology, social work, and chaplaincy team members; to support culturally meaningful practices; and to promote comprehensive pain care. Future research and collaboration with an interdisciplinary clinical and pastoral team are recommended to pilot test the conclusions in this review and to explore the development of an acute pain scale for SCD patients that may fully incorporate BPS-R/S factors.

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Figure 1: Overview of search methods of integrative review

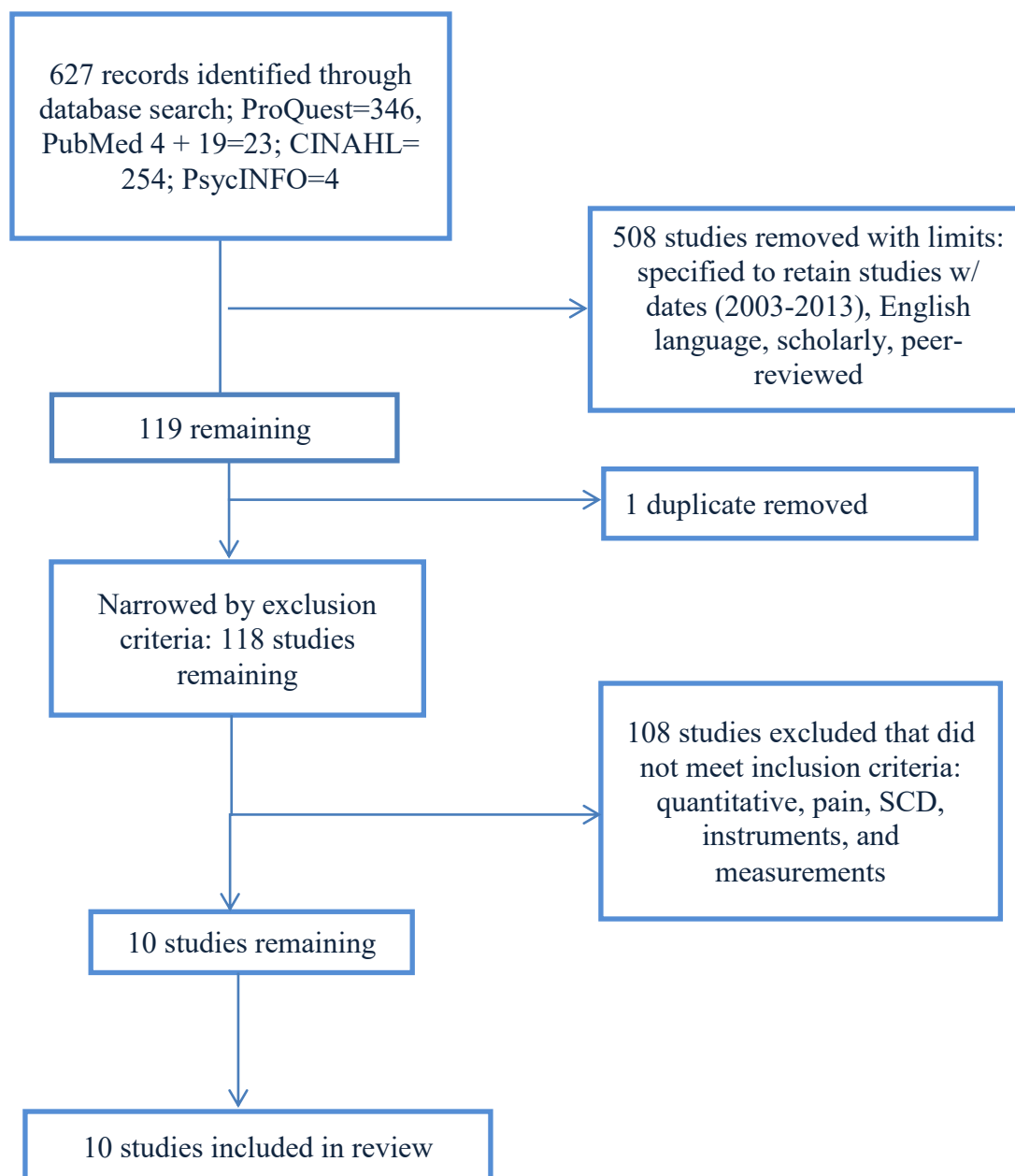


Table 1 – The biological, psychological, and sociological (BPS) dimensions of pain instruments			
Instrument	Biological	Psychological	Social
Unidimensional			
African-American ouch scale (AAOS)	X		
Numeric rating scale (NRS)	X		
Visual analog scale (VAS)	X		
Wong-Baker faces scale (WBFS)	X		
Multidimensional			
Brief pain inventory (BPI)	X	X	X
Sickle cell pain diary (SCPD)	X	X	X
Observable scale of behavioral distress (mOSBD)	X	X	
PAINReportIt (cMPQ = computerized MPQ)	X	X	
Short form-McGill pain questionnaire (SF-MPQ)	X	X	
Sickle cell disease pain burden interview-youth (SCPBI-Y)	X	X	X
X = indicates presence in study			

Table 2: Review of Instruments and Studies

Instrument(s) Reference(s)	Theoretical Framework	Description of Research Participants	Instrument Description	Validity	Reliability	Feasibility of using Instrument	Level of Evidence Grade OCEBM 1-5
Brief Pain Inventory short form (BPI-SF), Dampier et al., 2013	None reported	38 participants (4 withdrew) with all genotypes of SCD > 10 years of age w/acute pain rated as ≥ 45 on VAS	Multidimensional instrument; items using yes or no, identification of pain sites and a rating scale	None reported construct validity found in Atkinson et al., 2011 Correlation coefficients $p < 0.05$ Correlation of the SF-36 Mental Health scale is excellent with the various summary scores of the BPI: 7-item (Spearman's $\rho = -0.62$), 10-item (Spearman's $\rho = -0.60$), 12-item (Spearman's $\rho = -0.61$). [Raichle et al. 2006]	None reported Cronbach's α reliability ranges: 0.77-0.91 found in Atkinson et al., 2011 Internal consistency of the BPI is excellent for the 7-item scale (Cronbach's $\alpha = 0.92$), the 10-item scale (Cronbach's $\alpha = 0.95$) and the 12-item scale (Cronbach's $\alpha = 0.96$). [Raichle et al. 2006]	No cost for use of BPI instrument unless used commercially or for funded research; BPI-SF: self-administered completed in 10-15 minutes	2
Daily pain diary Smith et al., 2005	Biopsychosocial (BPS) Conceptual Explanatory Model of Pain and Response to Pain in SCD & Health Belief Model	300 eligible participants with SCD Age 16 years or older Living in VA Inclusion: patients able to communicate by phone and complete the diary Exclusion: patients with MMSE < 27 or those on chronic exchange transfusions	Multidimensional instrument; participants rate & record their pain, distress and disability on an ordinal scale from 0-9.	Face validity discussed; Pain diaries have been used with success in this population (Gil, Carson & Sedway, 2000) No validity data reported.	None reported	Pain diaries rely on subject to complete and return to reviewers; clear guidelines about diary submission schedules and the importance of providing support and structure to facilitate their participation. The design has limits to use of this instrument based on age and ability.	2
Numeric Rating Scale (NRS) Myrvik et al., 2013	None reported	28 participants Age 8-18 years Mean age 14.65 years 14 males 14 females Inclusion: any genotype of SCD receiving analgesic treatment for uncomplicated VOC; English primary language	NRS is a unidimensional instrument; 11-point scale, 0-10 NRS patient identifies a number by writing down a number between 0 and 10 that relates to their pain	None reported	None reported	Ease of administration, no cost	2

Zempsky et al., 2013b	None reported	25 participants Age 11-20 years 5 males 20 females Race: Black 76% White 8% More than 1 race 12% Ethnicity: Non-Hispanic 84% Hispanic 12% Not reported 4%	NRS is a unidimensional instrument; 11-point scale, 0-10 NRS patient identifies a number between 0 and 10 that relates to their pain.	Referenced validity from Bailey et al., 2010; Von Baeyer et al., 2009	None reported	NRS 11-item scale, simply and quickly administered	2
Observable Scale of Behavioral Distress (mOSBD) McClellan et al., 2009	None reported	48 participants w/ SCD receiving venipuncture as part of routine health maintenance visits Ages 2-17 years Mean age 9.6 years 3 age groups: 2-4, 5-9, & 13-18 years 24 males 24 females	mOSBD: a multidimensional instrument; children were videotaped to assess presence or absence of 11 behavioral indicators of procedural distress, used raters to monitor video recordings of observed pain experiences & behavior to determine the level of distress associated with a painful medical procedure. The 2 raters were trained with 93-100% interrater agreement	Criterion validity of 1st hypothesis $r = 0.49$ $p < 0.01$ 3 age groups: $t = (11) = 3.86$, $p < 0.01$; $t = (12) = 1.94$, $p < 0.05$; $t = (18) = 2.12$, $p < 0.05$	Instrument reliability: Cronbach's alpha range 0.68 to 0.72 Reported as a reliable, valid instrument (Jay et al 1983).	This scale requires extensive training and assessment of trained individuals for interrater reliability	2
PAINReportIt , A computerized extension of the McGill Pain Questionnaire (MPQ) Wilkie et al., 2010	None reported	145 participants with SCD Age <u>18 years or older</u> AA 93.8%, White 1.4%, Hispanic 2.8%; More than 1 race 2.1% Participants received outpatient care at SCD clinic, pain > 3 on a 0-10 scale	Multidimensional instrument that measures pain location, intensity, quality & pattern PAINReportIt-Plus-ABQ software is computer extension of the McGill Pain Questionnaire (MPQ)	Referenced validity in Using PAINReportIt instrument in persons with SC from Jha et al., 2010 Reported 30 year research history using MPQ to establish its validity	Cronbach's alpha for internal consistency reliability + .63, .77, .75; in the Barrier portion of the questionnaire. Reported 30 year research history using MPQ to establish its reliability.	Pen-tablet computer required; subjects were given 'standardized' practice before beginning; Feasibility was measured using a computer acceptability scale (CAS) 0-13 ranking PAINReportIT total time: Mean 21.4 minutes Range = 0.1 – 57.5 minutes	2

<p>Short Form-McGill Pain Questionnaire (SF-MPQ) A Paper format</p> <p>Edwards et al., 2006</p>	<p>Social Learning and Modeling Theory</p>	<p>67 Adult participants Ages 18-70 years 30 males 37 females Race not identified</p> <p>Enrolled in Duke Comprehensive Sickle Cell Center</p>	<p>SF-MPQ – A multidimensional instrument; subjects rate the current intensity of each pain adjective by circling: none, mild, moderate, severe</p>	<p>None reported</p>	<p>SF-MPQ: None reported for current study.</p> <p>Found test –retest reliability per intraclass correlations of 0.96, 0.95, 0.88, & 0.89 in sample w/o SCD in Grafton, Foster and Wright , 2005</p>	<p>SF-MPQ: no feasibility data reported</p>	<p>2</p>
<p>The Sickle Cell Disease Pain Burden Interview –Youth (SCPBI-Y)</p> <p>Zempsky et al., 2013a</p>	<p>None reported</p>	<p>62 outpatient English-speaking participants; Ages 7-21 years Mean = 15.30 years</p> <p>33.9% male, 66.1% female</p> <p>80.6% Black 11.5 % Hispanic during acute pain</p> <p>67 inpatient English speaking participants 7-21 years M = 15.70 43.3% male; 56.7% female; 89.7% Black 6.1% Hispanic</p>	<p>SCPBI-Y- A 7-item multidimensional Likert- type instrument (none = 0, few = 1, some = 2, many = 3, every = 4</p> <p>Designed to assess impact of pain on physical, social /community, & emotional aspects of daily function.</p> <p>Range 0-28 (0 = no pain burden to 28 = severe pain burden)</p>	<p>SCPBI-Y- Reported strong construct validity demonstrated by a positive relationship between higher pain burden and increased painful days in outpatient group</p> <p>Construct validity was determined by comparing inpatient and outpatient groups; pain burden was greater in the inpatient group (t[127] = -5.12, p < 0.001)</p>	<p>SCPBI-Y- Cronbach's α .909 O//P group; .821 I/P group and .891 in both, via test-retest reliability using Pearson correlation coefficient $r = .80, P < 0.001$</p>	<p>Can be completed by patients and caregivers in 1 minute Specifically measures pain burden</p>	<p>2</p>

Visual Analog Scale (VAS) Luffy and Grove, 2003 (L&G)	None reported	100 participants with all genotypes of SCD Age groups: 3-7, 8-12, 13-18 years	VAS – Unidimensional instrument; 1 item scale Scored on a 100 mm pain intensity scale 0 mm = no or least pain 100 mm = “pain as bad as it could possibly be”	Reported construct validity $r = 0.44, 0.28, 0.44, p < 0.001$ (between parent & child, nurse & child, nurse & parent) from Pothmann, 1990	Reliability, interrater reliability 90%; $r = 0.87$; test-retest agreement = 29% Adjusted reliability = 45%	VAS - 1 item scale, simply and quickly administered to wide range of age groups; however, preschool age groups have difficulty using this instrument	2
Edwards et al., 2006	Social Learning and Modeling Theory	67 adult participants Ages 18-70 years 30 males 30 females Enrolled in Duke Comprehensive Sickle Cell Center Race not identified	Patient or proxy marks the place on line Line is then measured and scored between 0 and 100; (often translated to a 0-10 rating)	VAS $p = 0.008$	None reported		2
McClellan et al., 2009	None reported	48 participants with SCD Ages 2-17 years Mean age 9.6 years 3 age groups: 2-4, 5-9, & 13-18 years 24 males 24 females Receiving venipuncture as part of their routine health maintenance visits in Columbia, SC	0-100 scale. Included patient and parents rating of patient's pain	Reported criterion and convergent validity of parent report of child's pain using VAS: $R = 0.72, p < 0.001$ from Varni, Thompson and Hansen, 1987	Child report $r = 0.33$; for parent report of children (age 2-4 years) $r = 0.27$		2
Dampier et al., 2013	None reported	38 participants (4 withdrew) with all genotypes of SCD greater than 10 years of age w/acute pain rated as ≥ 45 on VAS	0-100 scale	None reported	None reported	Identified ease of administration in older child and adult populations	2
Myrvik, et al., 2013	None reported	28 participants Ages 8-18 years Mean age 14.65 years 14 males 14 females Inclusion: any genotype of SCD receiving analgesic treatment for uncomplicated VOC; English primary language	0 = no pain -10cm worst possible pain (scale)	None reported	Used receiver operating characteristics (ROC) curve analyses; areas under the curve (AUC) were used to assess the accuracy and discrimination of VAS to assess pain. VAS was found to be a fair discriminator (0.70-0.80)	Serial assessment using VAS every 30 minutes while in ED	2

<p>Wong-Baker FACES Scale (WBFS)¹</p> <p>Luffy and Grove, 2003</p>	<p>Leininger's Theory of Nursing Cultural Care Diversity and Universality, 1988</p>	<p>100 African American children w/SCD Ages 3-18 years Mean age 8.52 years 51% males 49% females Divided into 3 age groups (Piaget cognitive periods): Ages: 3-7, 8-12, & 13-18 years</p>	<p>WBFS – Unidimensional instrument; rated 0-5; 6 pictures of faces from smiling face to crying face; pictorial scale used for children > 3 years old</p>	<p>Reported WBFS concurrent validity of $\chi^2 = 1.21$, $df = 5$; from Wong & Baker, 1988 in Luffy and Grove</p> <p>Reported $r = 0.63$ to 0.94 from Keck et al. 1996</p>	<p>Intrater reliability 90%; test re-test reliability 37%; adjusted reliability to 67% Reported convergent reliability $t = .67$ & $p = .0001$ from West et al., 1994 Reported reliability $r = 0.791$ from Wong and Baker, 1996</p>	<p>WBFS – 6-item scale, simply and quickly administered</p>	2
<p>Frei-Jones, Baxter, Rogers, Buchanan, 2008</p>	<p>None reported</p>	<p>8-19 year olds with uncomplicated VOC</p> <p>123 males 156 females</p> <p>Race not identified</p>	<p>0-5 Faces scale pictorial used for children > 8 years of age Subjects point to the face picture that best rates the pain 0 = no pain, 5 = worst pain</p>	<p>None reported</p>	<p>None reported</p>	<p>Nurses provide WBFS in ED during initial triage & every 15-30 minutes after initial dose of morphine</p>	2
<p>McClellan et al., 2009</p>	<p>None reported</p>	<p>48 participants w/SCD Ages 2-17 years Mean age 9.6 years 24 males 24 females Inclusion: receiving venipuncture as part of their routine health maintenance visits</p>	<p>WBFS pain rating 0-5; 6 pictures of faces from smiling face to crying face</p> <p>Pictorial scale used for children > 2 years</p>	<p>Referenced validity from Bieri, Reeve & Champion, 1990; Luffy and Grove, 2003</p>	<p>Referenced reliability from Wong and Baker, 1988</p>	<p>WBFS preferred method of assessing pain in pediatric SCD citing Luffy & Grove, 2003</p>	2

Chapter 3

The Application of Genomic Testing for Pain Management in Sickle Cell Disease

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Abstract

Purpose/Objective: This literature review evaluates the current science of personalized medicine for sickle cell patients with refractory pain during vaso-occlusive episodes (VOEs) using genetic/genomic testing. The review intends to identify the importance of a working knowledge of genomics and pharmacogenomics to support safe practice, patient/family teaching, and advocacy.

Literature search: An examination of pain management strategies for persons with sickle cell disease (SCD) serves as the basis to learn and disseminate the knowledge of the genetics, genomics, and pharmacogenomics (PGx) related to sickle cell pain care. The Diffusion of Innovation (DOI) theory was used to assess strategies linked to innovation championing, colleague support, and adoption of genetic testing.

Findings: In 2014, the National Heart Lung and Blood Institute (NHLBI) supported the work of an expert panel that produced a synthesis of evidence-based protocols and algorithms to direct emergency department (ED) clinicians in the management of patients with SCD, including those with VOE. Addressing the knowledge gap in PGx will lead to linking strategies to decrease barriers to patient and provider understanding, as well as improve patient outcomes, develop comprehensive algorithms, and address reported dissatisfaction with ED care.

Conclusion: Genomics is an essential competency for nursing education and nursing science. This review seeks to expand the knowledge of PGx. Patients with SCD who demonstrate poor pain control despite compliance with existing evidence-based protocols may benefit from genomic testing and the newly introduced Precision Medicine Initiative (PMI) in the management of the pain and chronic disease.

Key terms: cytochrome P450, sickle cell, pain, pharmacogenomics, genetics, genomics, nursing

The Application of Genomic Testing for Pain Management in Sickle Cell Disease

Sickle cell disease (SCD) is a pleiotropic hematologic disorder affecting approximately 100,000 Americans (Centers for Disease Control and Prevention (CDC), 2015a; U.S. Department of Health and Human Services [USDHHS], 2014). One common genotype that causes red blood cells (RBCs) to sickle is hemoglobin SS (HbSS); in this scenario, the child inherits one sickle gene (S) from each parent (Anie & Green, 2012). Sickle-shaped RBCs result from the gene mutation of β -globin displacing glutamic acid with valine at the 6th position of the hemoglobin subunit (Ballas et al., 2010; Ghatpande, Choudhary, Quinn, & Goodman, 2008). Pain is the hallmark feature of SCD. Persons with sickle cell experience acute and chronic pain syndromes including “acute multiorgan failure, iatrogenic pain syndromes, neuropathy, and vaso-occlusive episodes” (VOEs) (Ballas et al., 2010, p. 7). The sickled cells in VOE cause obstructive ischemia (CDC, 2015b; Smith & Scherer, 2010; USDHHS, 2014) and tissue deprivation of glucose and oxygen. Episode frequency varies from person to person (Lettre et al., 2008). The painful episode can last from hours to days or longer, the complications are systemic, and there are intermittent and intractable VOE patterns of occurrence (Ballas et al., 2010; Ballas 2014; Human Genome, 2005). The incidence of VOE varies from one to several per year depending on disease severity (Ballas, 2014; Brousseau, McCarver, Drendel, Divakaran, & Panepinto, 2007). Patients experiencing VOEs seek health care services in emergency departments (ED) and often require management of dehydration, infection, and severe pain by emergency medical teams (Po et al., 2012).

Genotyping of persons with SCD provides information about medication biotransformation, which can facilitate precise, personalized health management. Identifying individual variability with genomic testing to improve patient outcomes is an essential

component of the upcoming Precision Medicine Initiative (PMI) (Collins & Varmus, 2015; Crews, Hicks, Pui, Relling, and Evans, 2012). The purpose of this manuscript is to advocate for the use of genetic testing to assist providers in personalizing treatment for sickle cell patients. The Diffusion of Innovation (DOI) theory can be used to inform the interpretation and dissemination of evidence regarding genomic testing of persons with SCD in order to ensure optimal treatment and patient outcomes.

Traditional Treatment Approaches

Po et al. (2012) reported that patients entering the ED for VOE and pain management benefitted when they had a healthcare team educated in the care of patients with SCD. When the provider utilized a standardized pain assessment instrument, patients were assessed in a timely manner, and the time to analgesic administration was less than 30 minutes. Additionally, febrile patients with SCD and chest pain syndromes were provided fluids and antibiotics along with timely vaccination of pneumonia and influenza preventatives (Po et al., 2012).

Inadequate care for patients experiencing VOE is common. Factors such as provider perceptions that patients may be drug-seeking can delay prompt healthcare services. Patient dissatisfaction and mistrust result when patients hear labels from their providers such as ‘substance abuser’, ‘clock-watcher’ and ‘frequent flyer’ (Jacob, 2001; Jenerette & Dixon, 2010). Social, cultural, and linguistic differences can lead to inadequate care (Po et al., 2012). Another factor in inadequate care for VOE includes trial and error measures to manage pain in the population with SCD, and divergence from care standards (Glassberg et al., 2013). The treatment standards include intravenous fluids, antibiotics for bacterial infections, non-opioid, and opioid medications (Ballas 2014; Glassberg et al., 2013; Lottenberg & Hassell, 2005; Myers & Eckes, 2012).

Literature Search

The search strategy for this review was developed in consultation with a research librarian. A search was conducted for studies in the following databases: National Library of Medicine (PubMed), Ovid, EBSCO Host containing the Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Scopus. The following key terms were used in each of the databases: cytochrome P450, sickle cell, and pain. The search of the 4 databases yielded a total of 82 results; 12 were retained for inclusion in this review (see Figure 1). The exclusion criteria were limited to English language studies and reviews involving human samples. In the PubMed search, the key terms yielded 8 studies, 2 were removed after a review of the abstracts. One was a study conducted on transgenic mice; the other did not contain information relevant to key terms and topic. In the Ovid database, the key terms yielded 53 results, of which 50 contained abstracts or the respective data pertained to only one aspect of the key subject matter. Three studies were retained. An EBSCO Host search using the key terms yielded 7 results all of which were duplicates of the Pub Med search. The Scopus search using the key terms yielded 14 results; 6 were duplicates of the Pub Med search, 5 were not specific to the topic, and 3 were retained for relevance to subject. See Figure 1 for an overview of literature search.

Genetics & Pharmacogenomics

Persons with SCD who have genomic variations may not obtain the intended pain relief from opioid therapy (Yee et al., 2013). The varying ability to metabolize and respond to the opioid agent is known as interindividual variability. The genomic variations that prevent efficacy of opioid agents during VOE may be explained by the principles of pharmacogenomics. Discovery of the structure and function of genes improves predictions of the genetic effects and individual responses to medication (Ballas 2014; Blix, 2014; U.S. National Library of Medicine,

2015). Two important genes, cytochrome P450 (CYP2D6) and UDP glucuronosyltransferases (UGT2B7), produce enzymes needed to metabolize opioid agents, a mainstay of VOE pain management (Ballas, 2014; Dabari, Minniti, Rana, van den Anker, 2008; Jimenez & Galinkin, 2015).

Pharmacogenetics and pharmacogenomics are synonymous terms used to describe a science that merges pharmacology and genomics. For the remainder of this review, pharmacogenetics and pharmacogenomics will be connoted as PGx. Nursing education that includes genetics and genomics at the undergraduate, graduate, and postgraduate levels prepares registered nurses (RNs) to function more fully in their professional roles. Use of genomics contributes to health assessment, screening, management, patient/family education, and advocacy (Daack-Hirsch, et al., 2013). RNs who are in graduate programs and who are planning to utilize prescriptive authority will improve their ability to prescribe medications safely based on their knowledge of the evolving PGx science (Krau, 2013). While some clinicians may not take genomic variation into account during their treatment of VOE, nurses educated in genetics and PGx are keenly situated to address this problem (Adegbola, 2010). They do this when they (a) assess SCD pain, (b) administer pain medication, (c) reassess efficacy of the pain medication intervention, and (d) evaluate whether the individual patient is experiencing the intended therapeutic effect. The application of clinical genomics may result in utilization of a more appropriate therapeutic agent, optimization of health outcomes, and reduction of adverse drug events (Calzone et al., 2013; Krau, 2013). A determination of proper dose and medication choice could be made pertinent to the patient's human genomic biomarkers and metabolic activity (Frueh et al., 2008).

To better serve patient populations with the existing scientific evidence, knowledge of personal genomic status is necessary through preemptive testing (Bielinski et al., 2014; Jaja et al., 2015). Current testing includes next generation genome sequencing assays such as, “whole-exome or whole-genome sequencing tests and copy number variant arrays” (Evans, Burke, & Jarvick, 2015, p. 2259), polymerase chain reaction (PCR) (Genelex, 2014; Althea Diagnostics, 2015; Food and Drug Administration [FDA], 2013) and single nucleotide arrays to detect variants of cytochrome P450 and UDP glucuronosyltransferases. Typically, samples of buccal cells are collected, with results available in 48 hours (Althea Diagnostics, 2015). Genetic variants affect the patient’s ability to derive the intended analgesic benefits of opioid medications during painful VOs (Ballas, 2014; Genelex, 2014; Lynch & Price, 2007). Variant labels include the following phenotype classifications: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM) (Ballas, 2014; Jaja, et al., 2015; Jimenez & Galinkin, 2015; Krau, 2013). EMs are considered normal metabolizers, and standard dosing has been developed for the EM group. Several studies have cited the serious nature of adverse reactions to medications. In the U.S., there are approximately 100,000 deaths per year due to serious adverse drug reactions and a corresponding financial burden in the billions of dollars (Ajayi, Sun, Perry, 2000; Collins, 2010; Wilke et al., 2007). The information obtained from genotyping can be used to reduce adverse drug reactions and their associated human and economic costs to patients and society by assisting the clinician in making a more appropriate choice of medication and dose for pain management and other pathologies (Ballas, 2014; Bielinski et al., 2014; Duconge & Rúaño, 2012; Jaja et al., 2015; Jimenez & Galinkin, 2015; Krau, 2013; Lynch & Price, 2007; Yee et al., 2013).

The FDA has recommended genetic testing for Warfarin, Valproic Acid, Dapsone, and Azathioprine therapies. When the following chemotherapeutic agents, Cetuximab and Trastuzumab are prescribed, testing is required (Frueh et al., 2008). Several medications used for persons with SCD rely on the polymorphic cytochrome P450 enzyme system for metabolism; however, genotyping persons with SCD for CYP450 or UGT2B7 to determine the best opioid management is currently not approved by insurance providers (Ballas, 2014). If clinicians knew the genomic status of their sickle cell patients, changes could be implemented to ensure that patients receive appropriate treatment (Jannetto & Bratanow, 2010; Polymorphism, n.d.). Provider knowledge of each person's genetic status associated with CYP450 has significance for patients by ensuring appropriate pain management and economic implications by decreasing inpatient hospitalizations associated with VOE (Yee, 2013).

Adult sickle cell patients receive inadequate treatment of VOE, leading to unnecessary suffering (Ender et al., 2013; Jenerette & Brewer, 2010). There are disparities in the quality of care delivered to SCD patients in the ED (Haywood, Tanabe, Naik, Beach, & Lanzkron, 2013; Jenerette & Brewer, 2010). The incidences of inadequate care may be reduced by PGx science, which can help to explain why certain therapeutic agents yield poor or adverse results. When sickle cell patients do not experience the intended benefits from standard opioid agents, e.g. Codeine and Hydrocodone, or from the nonsteroidal anti-inflammatory drugs (NSAIDs) class such as, Ibuprofen and Ketorolac, genotyping may explain the varied efficacies. When a primary care provider has the personalized genetic information, the patient can anticipate a better pharmacotherapeutic response (Jaja et al., 2015), which in turn may help to decrease the reported dissatisfaction with ED pain control. Knowing the patient's CYP2D6 and UGT2B7 metabolic status also will ameliorate concerns that providers may have regarding proper medication,

dosage, and appropriate frequency (Darbari, Minniti, Rana, van den Anker, 2008). Because they require long-term pharmacotherapeutic interventions, persons with SCD will benefit from the impact of evolving PGx science on the development of medications pertaining to the “genetic determinants of treatment effects” (Zineh & Pacanowski, 2011, p.730).

Application of Diffusion of Innovation

Everett Rogers developed the mid-range theory, Diffusion of Innovation (DOI). The DOI theory suggests that when stakeholders communicate consensus about an innovation, adoption of the innovation is likely to occur within regulatory guidelines. Health system stakeholders such as the FDA have oversight of genetic testing (Zineh & Pacanowski, 2011). The CDC and the Centers for Medicare and Medicaid Services (CMS), in collaboration with the FDA, reinforce the use of clinical laboratory improvement amendments (CLIA) quality control standards for laboratories performing genetic testing (CDC, 2015c). The oversight of genetic testing is still evolving and complex, and theories like the DOI can help clarify when to use genetic testing.

Even though Rogers may not have anticipated the scenario currently under investigation, DOI theory, as articulated by Rogers (2003), suggests that when stakeholders communicate the innovation, in this case genomic testing, consensus can result in adopting the tests. Genomic analysis has yet to be implemented to ensure appropriate pain management in the population of sickle cell patients. Scientific research supports further analysis and “preemptive genotyping” in persons with SCD (Jaja et al., 2015, p.272; Jaja, Patel, Scott, Gibson & Kutlar, 2014). Utilization of genomic testing and further analysis of its use may lead to personalizing treatment according to the individual’s needs, thus enabling providers to prescribe more accurate treatment.

Applying the Diffusion of Innovations to Sickle Cell

The adoption of pharmacogenomics practice by treatment centers, providers, and patients is an innovation that will help to remove barriers to the therapeutic effectiveness of a broad range of medications and demonstrate the clinical usefulness of genetic and genomic testing (Althea Diagnostics, 2015; Ballas, 2014; Blue Cross Blue Shield (BCBS), 2010; Calzone et al., 2013; Genelex, 2014; Jimenez & Galinkin, 2015; Krau, 2013). PGx is being used on a limited basis to assist in prescribing medications. To move towards the goal of personalized medicine and the Precision Medicine Initiative, preemptive genotyping also could be advantageous to the caregivers of individuals requiring long-term medication management. Knowing the genomic profiles of persons with sickle cell provides clinicians with integral component to a patient's health assessment. Linking all applicable health information supports safe practice and can result in greater provider and patient satisfaction. Above all, such information linking can improve outcomes and save lives (Zineh & Pacanowski, 2011).

The ED of hospitals is the entry point for care of patients experiencing a sickle cell crisis. Laboratory staff can perform genetic testing in certified laboratories by obtaining an oral swab, saliva, or a blood sample. Currently, genotyping takes 48 hours (Althea Diagnostics, 2015). Existing care protocols can be implemented until the genomic findings return; then a more educated and informed approach to care can occur, which will empower providers with a broader understanding of patients' needs. The patients can receive their personal health care data via health educators (geneticists, nurses educated in genetics/genomics) in the system. This information can become part of the electronic medical record (EMR), which will greatly assist in treating similar future crises. Patients' health needs will be improved by more targeted therapy, thereby potentially increasing patient satisfaction with services.

Policy change requires substantiated research evidence, as well as clinicians within the system who possess the knowledge and ability to influence and support stakeholders. Leaders are needed who will monitor data pertaining to the innovation and promote data progress, maintenance, and sustainability to ensure successful dissemination and application of the system change (Glanz, Rimer, & Viswanath, 2008; Rogers, 2003). Using the DOI's system-based approach, Carpenter and Sherbino (2010) described change promotion in a group of physicians who prioritized (a) seeking opinion leaders to help change standard care and (b) incorporating a new care standard to promote better patient outcomes. The researchers determined that, without such leadership, it may have taken 10 years to incorporate a new standard of care, even with authenticated evidence supporting the change.

According to an administrator of a representative emergency department, the changing of emergency care policy or protocols entails a process of sufficient study that is communicated by evidence pertaining to best practices of healthcare professionals. Accrediting bodies or established organizations such as The Joint Commission, Boards of Nursing (BON), Emergency Nurses Association (ENA), or other trauma coordinators organizations (TC) are influential in supporting the change. A medical director and members of the ED committee communicate the information to a clinical operations committee for consideration before adoption occurs (V. Oge, personal communication, 11/21/2012).

In addition to the complexity of creating change in the healthcare system, the patients' reluctance to change can contribute to innovation complexity, e.g., individuals may have reservations about their genetic information becoming part of their medical record. To help explain the benefits of genetic testing, more geneticists or genetically educated clinicians are

needed to inform patients about genetic testing and their legal protections under the Genetic Information Nondiscrimination Act (GINA) (Allain, Friedman, & Senter, 2012).

Finally, use of genomic testing for optimal medication selection is considered highly desirable, yet still in its early stages. Such testing will provide a forum for examination, experimentation, data collection, and dissemination of data, thus promoting value in treatment. Researchers have advocated for large prospective clinical trials to determine the efficacy of genotyping in the clinical environment (Lynch & Price, 2007). Pharmacogenomic testing is a timely scientific innovation that has significant potential to impact the public's health and to improve current health assessment, treatment strategies, and outcomes. In the United States (U.S.) today, there is growing support of system-wide initiatives to improve patient outcomes by government agencies, private institutions, and hospital organizations while also protecting patient and family confidentiality. Academic institutions, insurance corporations, medical and government-funded research centers are participating in the dissemination of information about genetic testing. However, genotyping and PGx continue to lack the substantive backing that could lead to better research analysis and implementation in practice (BCBS, 2010). In order to reach large audiences of researchers, clinicians, administrators, and policymakers, the translational benefits of such testing needs to be communicated to professional associations and accrediting organizations. Genetic testing is recommended or required practice in few circumstances despite substantial amounts of research about its use. From a patient advocacy and researcher standpoint, PGx can be used by clinicians as a guide for targeted treatment rather than hit or miss prescriptive practices (Krau, 2013). In a 2007 study, Brousseau, McCarver, Drendel, Divakaran, and Panepinto, assessed children with SCD that were unresponsive to codeine due to single nucleotide polymorphisms (SNP) of CYP2D6. Based on their analyses,

additional genetic testing and alternative medication therapies were recommended for the treatment of sickle cell pain (2007).

Nurses Role in Advancing the Innovation

Nurses are in an excellent position to educate patients with sickle cell disease and the community about genetic variability and pharmacogenomics (Adegbola, 2009; Jenkins, Prows, Dimond, Monsen, & Williams, 2001; Umberger, Holston, Hutson, & Pierce, 2013). The study of personalized medicine through genotyping and PGx is evolving. The implications for nursing education and practice have been studied, and nurse leaders, educators, researchers, institutions, and healthcare organizations have advocated genetics and genomics educational standards for baccalaureate and graduate prepared nurses (Consensus Panel on Genetic/Genomic Nursing Competencies, 2009; Daack-Hirsch et al., 2013; Umberger, Holston, Hutson, & Pierce, 2013; Williams et al., 2011). Various nurse scientists also have provided recommendations for inclusion and integration of genetics and genomics in nursing education (Daack-Hirsch et al., 2013; Daack-Hirsch, Dieter, & Quinn Griffin, 2011; Daack-Hirsch, Driessnack, Perkhounkova, Furukawa, & Ramirez, 2012; Hetteberg & Prows, 2004). An accrediting organization for nursing programs has endorsed genetic and genomic curriculum as essential components for nursing practice in the areas of diagnostics, assessment, and disease management (AACN, 2008).

A global nursing organization, the International Society of Nurses in Genetics (ISONG), promotes the educational and professional development of nurses in genetics and genomics by holding annual conferences, providing online and text resources (ISONG & American Nurses Association [ANA], 2007) and information pertaining to educational programs at the ISONG website (<http://isong.wildapricot.org/>).

Practicing nurses report the need for continuing education and the importance of having their professional organizations and opinion leaders as valuable resources in facilitating the safe integration of the evolving genetic and genomic science into nurse practice environments (Andrews, Tonkin, Lancaster, & Kirk, 2014; Coleman et al, 2014; Umberger, Holston, Hutson, & Pierce, 2013). Recently, the National Institute of Nursing Research (NINR) convened with other partners to develop a plan to guide and advance genomic nursing science over the next 10 years, with the goal of developing strong evidence to improve patient outcomes (Tully & Grady, 2015).

This review focuses on supporting the pain needs of persons with SCD and the benefits associated with genotyping. Persons with SCD take maintenance medications for chronic pain as well as medications for the acute exacerbations of VOE. PGx aids in ensuring that the right medication and the right dose are prescribed for the right person. There is increasing public awareness about genetic and genomic science. Nurses will be called upon to interpret what the genetic science means. When nurses draw upon their academic preparation and therapeutic communication skills to explain genetic testing and PGx, nurses fulfill their role as patient educators and advocates. When individuals know their personal genomic status, they can be empowered to self-manage their health. This exchange of knowledge and patient education is central to nursing practice in the 21st century.

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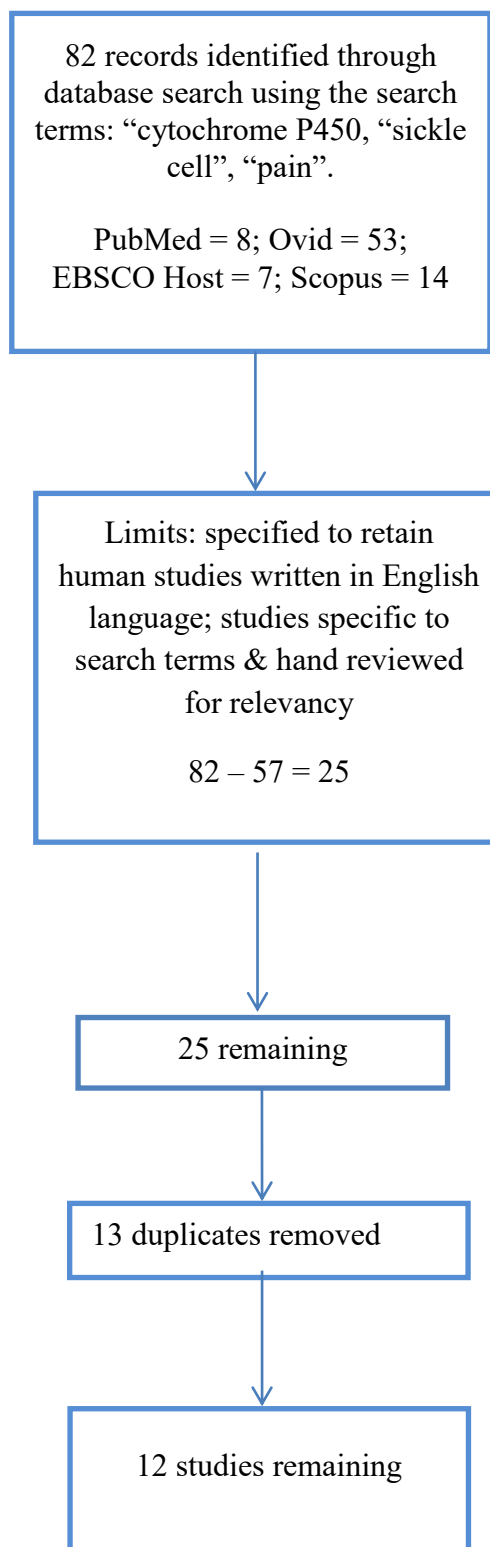
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Figure 1: Overview of search methods of literature review

Chapter 4

Associations of Psychosocial Measures with Quality of Life in a Sample of Adults with Sickle

Cell Disease

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Abstract

The exacerbations of sickle cell disease (SCD) impose significant disease burden on the persons affected. Currently, there is an absence of sickle cell specific evidence-based practice guidelines addressing the psychosocial health needs in this population though studies suggests that these needs are significant.

Using a quantitative approach, this study is a secondary analysis of data collected from adults with SCD (N = 179) in 2004 in the southeastern United States. The purpose of this analysis is to examine the associations of depressive symptoms (DS), self-efficacy, social support, coping and the coping subscale measures of spirituality with quality of life in this convenience sample.

The analysis identified a statistically significant association of depression, coping, self-efficacy and social support with quality of life in this sample.

Guidelines inclusive of the psychosocial health issues of persons with SCD support caregiver efforts to provide patient-centered care. Psychosocial health is a significant component of health-related quality of life and should be considered in the provision of holistic care.

Keywords: Sickle cell, psychosocial, mental health, secondary analysis

Associations of Psychosocial Measures with Quality of Life in a Sample of Adults with Sickle Cell Disease

Sickle cell disease (SCD) currently affects approximately 100,000 Americans (Centers of Disease Control [CDC], 2011). SCD is a genetic disorder that causes mutations to the hemoglobin molecules in red blood cells. These mutations cause vascular occlusions, infarctions (Nussbaum, McInnes, & Willard, 2007), and other acute and chronic pathologies. The chronicity and acute manifestations of the illness trigger severe recurrent pain episodes with physical and psychosocial debilities, including affective disorders such as depression. In persons with SCD, depressive symptoms (DS) are highly prevalent, ranging from 26 - 44% in salient studies (Edwards et al., 2009; Hasan, Hashmi, Alhassen, Lawson & Castro, 2003; Jenerette & Murdaugh, 2008). In comparison, the estimated prevalence of depression in the nation is 8% (CDC, 2012). Depression exacerbates chronic illnesses like SCD by increasing disease burden and disability (Moussavi et al, 2007). The incidence of suicide in the population with SCD is commensurate with other populations with severe chronic illness (Edwards et al., 2009), yet for individuals with SCD and its unique disease management requirements (e.g. pain control, health-related stigma, anxiety), evidence-based guidelines are absent for the screening and management of depressive disorders (Edwards et al., 2009; Jenerette, Funk, & Murdaugh, 2005; Thomas & Taylor, 2002; United States Department of Health [USDH], 2002, United States Department of Health and Human Services [USDHHS], 2014). Clinical practice guidelines exist for the management of psychiatric illnesses (APA Work Group on Psychiatric Evaluation, 2016). The lack of inclusion of such guidelines directly affects health management and may indirectly affect self-efficacy and quality of life in persons with SCD (Edwards et al., 2009; Jenerette et al., 2005; Thomas & Taylor, 2002; USDH, 2002).

This study examined the psychosocial needs of a sample of adults with SCD in order to identify factors predictive of quality of life in adults with SCD and to make inferences pertaining to targeted interventions. The purpose of this study was to identify the associations of psychosocial variables with quality of life by secondary analysis using the Self-Care Management for Sickle Cell Disease (SCMSCD) theoretical framework (Jenerette, 2004; Jenerette & Murdaugh 2008). This secondary analysis of 179 respondents with SCD (Jenerette, 2004; Jenerette et al., 2005; Jenerette & Murdaugh, 2008) offers information to establish the groundwork for future randomized controlled trials that provide needed evidence for the development of psychosocial clinical practice guidelines for comprehensive SCD care (United States Department of Health & Human Services [USDHHS], 2014).

Depression is characterized as a health outcome in the Self Care Management for Sickle Cell Disease (SCMSCD) model (Jenerette & Murdaugh, 2008). Blacks in the general population have a 10.4% lifetime prevalence of major depressive disorder (Edwards et al., 2009). Depression combined with chronic illnesses, like SCD, imposes additional burdens (Levenson, 2008; Moussavi et al., 2007; National Alliance on Mental Illness [NAMI], 2009; Thomas & Taylor, 2002). Chronic illnesses like SCD, combined with depression, are associated with decreased quality of life, self-efficacy, and health maintenance; also, susceptible individuals are more likely to experience a higher incidence of acute health crises (Levenson, 2008; NAMI, 2009; Thomas & Taylor, 2002). Providers can help patients with SCD better manage health complications by recognizing depressive symptoms (DS) early and facilitating prompt comprehensive health management (Tanabe et al., 2010).

In the parent study (Jenerette, 2004), 26% of the participating adults with SCD self-reported depressive symptoms at some point in their lives (SRDS), and the Beck Depression

Inventory Fast Screen (BDI-FS) demonstrated that 29% of the 179 respondents who completed the BDI-FS met the criteria for DS, as indicated in Table 1. The BDI-FS has reported approved psychometric ability to evaluate clinical change in patients with pain (Law, Naughton, Dhar, Barton, & Dabscheck, 2014; Poole, Bramwell & Murphy, 2009). In this study, the authors used the SCMSCD model to examine the associations between the sample's vulnerability factors and health outcomes, specifically depressive symptoms and quality of life. People with SCD experience stigmatization and disparate health issues related to acute and chronic pain, chronic illness management, psychosocial disorders, race, and inadequate provider knowledge. The patient population is in need of interventions that will facilitate provider understanding and support for patients' desires for self-efficacy and quality of life (Ballas, 2010; Haywood et al., 2009; Levenson, 2008; Tanabe et al., 2010). Vulnerability, intrapersonal factors, self-care management, and health outcomes are the foundation of the SCMSCD model. This study expand on the work of Jenerette (2004) by assessing DS along with self-efficacy, coping, and social support and its impact on quality of life.

Research Question. How are depressive symptoms (BDI-FS), sickle cell self-efficacy (SCSES), coping behaviors (FCPCS), social support (MOS-SSS), associated with quality of life (CIQOLL) in a sample of adults with sickle cell disease (SCD)? The following hypothesis guided the analyses: In an examination of depressive symptoms, quality of life will be affected when adjusted for disease related potential moderators self-efficacy, coping, and social support in a sample of adults with SCD.

Method

Data Source and Sample

The study sample for this secondary analyses consisted of 179 African Americans with SCD who completed measurements for depressive symptoms and quality of life. This sample is a subset of a convenience sample of 232 African Americans with SCD enrolled at two clinics from September 2003 through April 2004 in the southeastern U.S. to test the Theory of Self-Care Management for Vulnerable Populations in persons with SCD (Jenerette, 2004). The following inclusion criteria guided the selection of study participants in the original study: at least 18 years of age, able to read and write English, able to give consent, attending a sickle cell clinic, and having a diagnosis of SCD. University IRB, clinic approval, and informed consent were obtained before data collection occurred. Each of the participants received paper questionnaires that were completed within 45-60 minutes at one clinic visit. Twenty-five dollars were given to each of the subjects for participation in the research (Jenerette, 2004; Jenerette & Murdaugh, 2008). One hundred seventy-nine African American respondents completed both the CIQOLL and BDI-FS indicating their level of quality of life and depressive symptoms and are the subjects of this analysis.

Measures

The demographic data/health need vulnerability questionnaire is a 12-item survey that asked about age, gender, education, employment, marital status, number of vaso-occlusive episodes (sickle cell crises) per year that required hospitalization, and complications (Jenerette & Murdaugh, 2008).

The Family Coping Project Coping Scale (FCPCS) is a 54-item Likert-style survey instrument with the following five subscales that identify how a person copes, feels supported,

and manages health issues. The subscales are seeking/using social support, avoidance, spiritual activities, managing illness, and focusing on others. Exploratory factor analysis was used to determine construct validity, and Cronbach's alpha ranged from .71- .90, thus demonstrating internal consistency reliabilities. Coping behaviors are determined by the summation of subscale scores, with higher scores indicating a higher coping ability. (Jenerette, 2004; Jenerette & Murdaugh, 2008). Scores may range from 0 - 162. The subscale addressing spirituality was specifically examined. It contained 7 summed items with a potential scoring range of 0 – 21.

The Medical Outcomes Study Social Support Survey (MOS-SSS) is a 19-item Likert-style instrument that measures a person's perceptions of support. The four subscales are emotional/informational, affectionate, tangible, and positive social interaction. Confirmatory and principal components analysis supported construct validity with both total and subscales Cronbach's alpha of value of .91, thus establishing internal consistency reliabilities. Higher summed scores indicated greater social support (Jenerette, 2004; Jenerette & Murdaugh, 2008). Scores may range from 19 - 95.

The Beck Depression Inventory-Fast Screen (BDI-FS) is a 7-item scale used to screen individuals for DS in the clinic environment because of its conciseness. It is an abbreviated version of the BDI-II and is believed to be a culturally appropriate instrument for screening African Americans (Dutton et al., 2004). The BDI-FS demonstrated coefficient reliability in various practice settings. The reliability coefficient of 0.84 was calculated using Cronbach's alpha. Higher summed scores on the BDI-FS indicate greater depressive symptom severity (Jenerette et al., 2005). Scores may range from 0 - 21.

The Chronic Illness Quality of Life Ladder (CIQOLL) is a 28-item survey scale that subjectively measures the following seven aspects: physical, emotional, financial, family and

friends, spiritual well-being, peace of mind, and overall satisfaction or quality of life (Jenerette & Murdaugh, 2008). CIQOLL has demonstrated reliability and validity in measuring quality of life indicators in persons with chronic illness (Murdaugh, Moneyham, Jackson, Phillips, & Tavakoli, 2006). Cronbach's alpha coefficients ranged from .91- .95, and internal consistency coefficients surpassed the standard level of .80. A higher summed score on the CIQOLL indicates a better perceived quality of life (Jenerette & Murdaugh, 2008). Scores may range from 28 - 280.

The Sickle Cell Self-Efficacy Scale (SCSES) is a 9-item Likert-style scale that measures a person's views of how they are best able to live their lives with SCD. The scale measures the relationship between self-efficacy and (a) self-esteem, (b) sense of mastery, and (c) internal health locus of control to establish convergent validity. Cronbach's alpha was used to evaluate the internal consistency; a level of .89 was reported. The greater the summed score on the SCSES, the higher the perception of a well-managed life with SCD (Jenerette & Murdaugh, 2008). Scores may range from 9 - 45.

The reliability of each of the data collection instruments was determined to be .70 or greater, with one exception. The FCPCS subscale (focusing on others) had a lower reliability (.56), using Cronbach's alpha as a measure of internal consistency (Jenerette & Murdaugh, 2008). Jenerette et al. discussed conclusions and limitations of their research, which provided insight for this analysis (2008).

The levels of measurement for the categorical variables sex, employment, relationship status, housing status and self-report depression yes/no are nominal. Age, education, income, sickle cell crises per year are ordinal levels of measurement. The levels of measurement for the continuous variables-BDI-FS total, SCSES total, FCPCS total, CIQOLL totals, and MOS-SSS total are scale survey totals and nominal measures.

Statistical Analyses

The level of DS as determined by the BDI-FS total score was the primary independent variable (IV) of interest and was analyzed as a continuous variable. The CIQOLL- quality of life total score was used as the dependent variable (DV, continuous). The research question for this study follows: How are depressive symptoms (BDI-FS), disease-related self-efficacy (SCSES), coping (FCPCS), and social support (MOS-SSS) associated with quality of life (CIQOLL) in a sample of adults with SCD?

To investigate the characteristics of the study sample, univariate analyses were conducted for all demographic and psychosocial variables. Tests for data normality were conducted and assessed using Kolmogorov - Smirnov tests and Q-Q plots. The variables were approximately normal except for the number of sickle cell crises (vaso-occlusive crises) per year, and BDI-FS total scores, which were log transformed after adding a “1” to each score (or number of years) due to possible “zero” values.

Associations of quality of life with study variables were explored in a step-wise manner. In step 1, bivariate associations of the effect of the demographic, clinical, psychosocial variables on quality of life were examined using independent t-tests, and correlation as appropriate. Demographic and clinical variables that showed a p-value of 0.2 or less were included in subsequent regression modeling along with variables known or suspected to affect quality of life regardless of their significance in bivariate analysis. In a second step, multiple linear regression was used to investigate the association of quality of life (CIQOLL) with the primary variable of interest, log-transformed depressive symptoms (BDI-FS t) in combination with one additional psychosocial variable self-efficacy (SCSES), coping (FCPCS), spirituality (FCPS subscale) and social support (MOS-SSS). Subsequently additional psychosocial variables were added to each

of the previous models until all adjustment variables were included. Variables were retained in the final model even if no statistically significant association with quality of life was observed if they contributed to the variance explained in quality of life in the full model. The coping variable (FCPCS) in the bivariate was not statistically significant, p value .289, but was included in modeling due to suspected association with quality of life. Moderation among psychosocial variables was investigated by including interaction terms for moderation of the effect of depressive symptoms on quality of life through self-efficacy, social support, coping and spirituality as well as interaction terms of moderation between coping and spirituality with social support and self-efficacy.

Results

In this sample of 179 African Americans, with SCD the mean age was 34.1 years. Sixty-two percent were female, with a mean number of years of education of 12.4; 39.1% were unemployed and disabled, 65.9% were never married, and 72.1% lived with family. Most individuals were diagnosed with sickle cell disease in their youth and reported having 2 - 3 sickle cell crises per year. Fifty-two of the 179 participants or 29.1% had a BDI-FS score that met or exceeded the cut-point of four (Jenerette et al., 2005) indicating the likelihood of depression (Table 1). Demographic and clinical characteristics displayed no statistically significant associations with quality of life (Table 2).

In bivariate models, the individual psychosocial variables were statistically significantly associated with quality of life with the exception of coping and the spirituality coping subscale ($p = 0.289$, $p = 0.257$, respectively (Table 3). Higher self-efficacy, social support and fewer depressive symptoms were associated with higher quality of life. Depressive symptoms alone explained 25.6%, of the variance in quality of life (Table 3). No statistically significant

interactions were observed indicating that none of the psychosocial variables moderated the effect of depressive symptoms on quality of life in this sample. Similarly no moderation effect was observed among the psychosocial variables (all $p > 0.05$).

The final multivariate model, which included all psychosocial variables as main effects, resulted in 39.3% of the variance in quality of life explained when combined (Table 4). Though coping did not show a statistically significant association with quality of life in this model (p value = .316), when it was added to the final model the variance explained in quality of life (R^2) increased from .384 without coping in the model to .393 when coping was included. Spirituality was not included in the final model since it is a subscale of the coping scale and therefore included as part of the total score and did not show a statistically significant association with quality of life individually. Sick cell crises per year (SCC/yr.) had a statistically significant p value = .011; however, it was not included in the final model because it reduced the explained variance in quality of life. The final model included data from 105 individuals with complete information for all variables. The participants who were included in the analysis did not differ in terms of characteristics from those that were excluded due to missing data on one or more of the psychosocial questionnaires or adjustment variables except for income ($M = 37,207 \pm 9,773$ vs. $33,900 \pm 10,301$; $p = .036$), education ($M = 12.64 \pm 2.11$ vs 11.93 ± 1.93 ; $p = .024$), and age diagnosed with SCD (5.24 ± 6.28 vs 8.11 ± 8.28 ; $p = .013$).

Discussion

The aim of this secondary analysis was to examine the psychosocial influences including the effect of spirituality and identify factors predictive of quality of life in the sample of 179 African American adults with SCD. This genetic blood disorder affects all of the body's

systems, requiring comprehensive, patient-centered healthcare. This healthcare includes screening patients with SCD for psychosocial mental health disorders.

The level of depressive symptoms made the single strongest contribution to the variance explained in the dependent variable (CIQOLL) and proved to be a statistically significant predictor of quality of life (Table 3). The interaction of spirituality and depressive symptoms approached significance, p value = .066 indicating that further research with larger study samples focusing on spirituality is needed.

We hypothesized that quality of life, is affected by self-efficacy, coping, social support, and depression. This hypothesis was supported by the final model consisting of psychosocial factors explaining 39.3% of the variability in quality of life (Table 4).

The participants in the original study were asked to report complications of SCD; 26% of the sample identified depression as a condition experienced during their lifespan (Jenerette & Murdaugh, 2008). Depressive symptoms measured by the BDI-FS in the sample alone accounted for 25.6% of the variability in quality of life. Psychosocial characteristics, such as those identified clinically by the BDI-FS are modifiable and it is essential that depression is recognized and managed (Jenerette, Funk, Murdaugh, 2005; Jerrell, Tripathi, McIntyre, 2011). The benefits of treatment have far-reaching implications to the persons affected, their social support system, and the health system. These benefits include improved quality of life, increased social engagement, and decreased health system burden.

SCD is frequently associated with acute pain, which takes precedence over psychosocial treatment when patients are experiencing emergent pain needs. Chronic pain is a significant concern and is associated with underlying sickle cell pathologies. A relationship has been established between psychosocial factors and the chronic pain of persons with SCD.

Psychosocial health management using cognitive and behavioral therapies is an important adjuvant to chronic pain care (Edwards et al., 2005). Information to guide psychosocial health management is absent in current treatment guidelines. The development of patient-centered research to address these deficits is needed. In the interim, collaboration with psychology and social work disciplines in the assessment and treatment of persons with SCD to identify psychosocial health issues may benefit patients and providers.

Self-efficacy consistently showed a statistically significant association with quality of life in the bivariate and multivariate models regardless of additional covariates in the model. This implies self-efficacy is a meaningful predictor for quality of life. An association exists between one's perceptions of their ability to live life in spite of complexities (Thomas & Taylor, 2002). These implications statistically support that higher levels of self-efficacy associated with the ability to adjust to life circumstances may promote quality of life.

No statistically significant association was observed in this sample between quality of life and demographic characteristics related to housing status, relationship status, and employment. Social support and number sickle cell crises per year were associated with quality of life in bivariate analyses, however, this relationship did not hold in the multivariate model. Nonetheless, a lack of support for the aforementioned factors may make one vulnerable (Jenerette & Murdaugh, 2008) and sufficient evidence exists that suggests social support and pain management are vital to health maintenance and quality of life in persons with SCD (Edwards et al, 2005; Jenerette, 2008; Lanzkron & Haywood, 2015).

A pilot study to determine strategies that work best for clinicians and patients may be helpful in establishing grant funding for future research. Further inquiry of bio-psycho-social-spiritual and clinical characteristics targeting depression, quality of life, and self-efficacy as well

as spirituality are areas for future research. There are unidentified factors to explore since the model did not explain 60.7% of the variability in quality of life and further research is needed. Due to the nature of a secondary analysis, questions and analysis are narrowed to the data collected at the time of the original research. The selection of participants from a variety of regions in the United States would be reflective of a more representative sample. Despite these limitations, this dataset provides an opportunity for research in which new and relevant conclusions can be drawn to address the psychosocial needs of persons with SCD and further the goal of improving their quality of life.

Conclusion. This analysis demonstrates important associations among quality of life, depressive symptoms, self-efficacy, social support and coping as valuable predictors of quality of life in the sample of persons with SCD. The data associated with these findings need to be confirmed in prospective studies, if the findings hold, interventions may be developed to benefit persons with SCD. Psychosocial health management is a crucial element of each person's overall health and quality of life and evidence-based guidelines inclusive of the psychosocial domains may be beneficial to persons with SCD. (Prince et al., 2007; World Health Organization [WHO], 2014).

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Table 1: Demographic and psychosocial instruments N = 179

	N	Minimum	Maximum	Mean	Median	STD	Proportion
DEMOGRAPHICS							
<i>Age (yr.)</i>	179	18	73	34.1	30.0	12.5	
<i>Female</i>	111						62.0%
<i>Education (yr.)</i>	179	5	21	12.4	12.0	2.1	
<i>Income (\$)</i>	170	17843	65375	35865	35424	10092	
<i>Employment</i>	179						
<i>Fulltime</i>	37						20.7%
<i>Part-time</i>	18						10.1%
<i>Not employed</i>	54						30.2%
<i>Not employed - Disabled</i>	70						39.1%
<i>Relationship status</i>	179						
<i>Married</i>	34						19.0%
<i>Divorced</i>	12						6.7%
<i>Widowed</i>	8						4.5%
<i>Separated</i>	7						3.9%
<i>Never married</i>	118						65.9%
<i>Housing status</i>	178						
<i>Live alone</i>	37						20.7%
<i>Live with family</i>	129						72.5%
<i>Live with friends</i>	12						6.7%
CLINICAL CHARACTERISTICS							
<i>Age Diagnosed with SCD</i>	163	1	55	6.4	4.0	7.3	
<i>Sickle Crises per Year (SCC)</i>	169	0	25	2.6;	2.0	3.3	
<i>History of Self-Reported Depression</i>	48						26.8
PSYCHSOCIAL INSTRUMENTS							
<i>Chronic Illness Quality of Life Scale (CIQOLL)</i>	179	51	280	222.9	227.0	34.1	100%
<i>Beck Depression Inventory- Fast Screen (BDI-FS)</i>	179	0	19	2.7	2.0	3.4	100%
<i>Medical Outcomes Study-Social Support Survey (MOSSSS)</i>	157	31	95	76.0	77.0	15.1	87.7%
<i>Family Coping Project Coping Scale (FCPCS)</i>	117	56	156	101.5	99.0	20.4	65.4
<i>Sickle Cell Disease Self-Efficacy Scale (SCSES)</i>	175	12	45	31.6	32.0	6.9	97.8
<i>BDI-FS Indices</i>							
<i>0-3</i>	127						71%
<i>*4-6</i>	31						17.3%
<i>7-9</i>	10						5.6%
<i>10-19</i>	11						6.1%

*4 or greater cut-point for depressive symptoms

Sample size (N) varies due to missing data

Table 2: Association of demographic characteristics with quality of life (CIQOLL). N =179

Variable	N	CIQOLL			
		Mean	Standard Deviation	Correlation coefficient	p-value*
Gender					.472
Female	111	224.4	30.7		
Male	68	220.6	39.3		
Age	179			.025	.764
Age diagnosed with SCD	179			.014	.866
Education (yrs)	179			.004	.963
Employment					.590
Full time Employment	37	222.6	30.5		
Part time Employment	18	230.1	24.2		
Not employed	54	224.9	31.8		
Not employed, disabled	70	219.7	39.7		
Income	170			.118	.150
Relationship status					.366
Single, never married	118	222.0	37.1		
Married	34	223.5	25.9		
Divorced	12	223.1	38.0		
Widowed	8	231.3	15.5		
Separated	7	226.0	31.9		
Housing status					.809
Live alone	37	219.8	42.6		
Live with family	129	223.7	32.5		
Live with friends	12	224.5	24.6		

* p value from Pearson Correlation, independent T-test or ANOVA

Table 3: Bivariate linear regression models investigating the association of psychosocial characteristics individually with quality of life. (N=179)

Independent Variable	N	Beta-coefficient	Standard error	t-statistic	p-value	95% Confidence interval	Adjusted R ²
Beck Depression Inventory- Fast Screen*	179	47.1	5.96	-7.89	<.001	-58.8, 35.3	.256
Sickle Cell Disease Self-Efficacy Scale (SCSES)	175	2.24	.34	6.62	<.001	1.57, 2.91	.197
Family Coping Project Coping Scale (FCPCS)	117	.17	.16	1.07	.289	-.142, .471	.001
FCPCS spirituality subscale	164	.74	.65	1.14	.257	-.54, 2.02	.002
Medical Outcomes Study-Social Support Survey (MOS-SSS)	157	1.00	.15	6.62	<.001	.702, 1.30	.215
Sickle cell crises per year*	169	-1.99	.78	-2.57	.011	-3.52, -.462	.032

*Variables log transformed adding 1 to each score prior to transformation

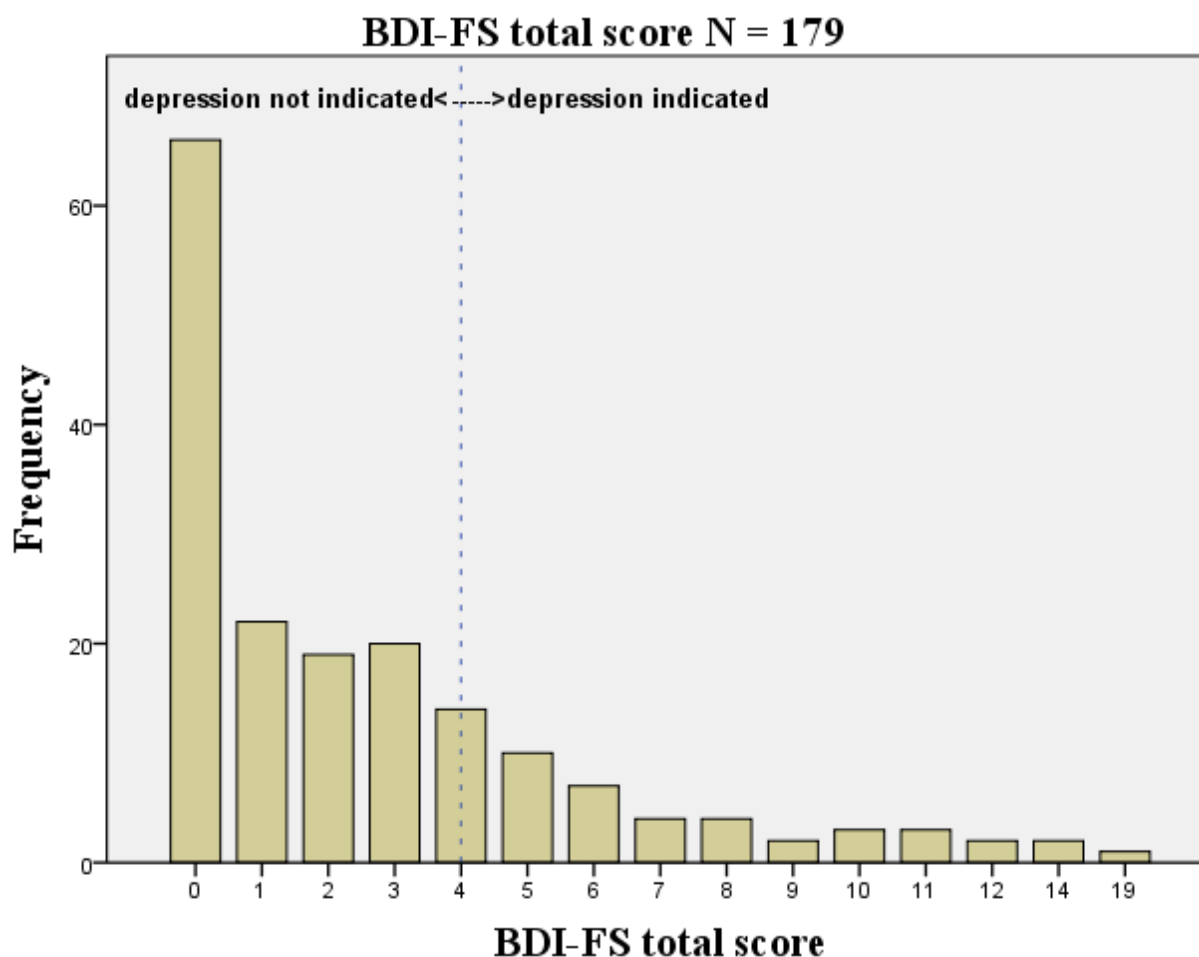
Table 4: Multivariate linear regression model including all psychosocial characteristics as independent variables and quality of life as dependent variable.

(Adjusted R² = 0.393; N = 179)

Independent Variable	Beta-coefficient	Standard error	t-statistic	p-value	95% Confidence interval
Beck Depression Inventory- Fast Screen*	-30.74	8.09	-3.80	<.001	-46.78, -14.70
Family Coping Project Coping Scale	.13	.13	1.01	.316	-.126, .384
Sickle Cell Disease Self-Efficacy Scale	.95	.44	2.15	.034	.075, 1.83
Medical Outcomes Study-Social Support Survey	.25	.19	1.35	.180	-1.19, .628

Variables log transformed adding 1 to each score prior to transformation

Figure 1. Frequency distribution of Beck Depression Inventory- Fast Screen



BDI-FS score of 4 - 19 indicate clinical concern. Beck Depression Inventory- Fast Screen BDI-FS scores 0–3 indicates minimal depression; 4–6 indicates mild depression; 7–9 indicates moderate depression; and 10–21 indicates severe depression Wang & Gorenstein, 2013.
*Cut Score of 4 is indicated by vertical dotted line.

Chapter 5

Dissertation Summary**Synthesis**

Sickle cell is an autosomal, recessive, single-gene disorder that has a 25% chance of being inherited by an offspring when both parents are carriers of a sickle cell gene. This illness has a significant impact on the person, family and community and requires the coordination of preventive care, chronic disease maintenance, and acute health management from early childhood throughout adulthood.

The three manuscripts of this compendium are interconnected because each focuses on persons with sickle cell disease as the population of interest or research sample, as well as, acute pain, pain management, disease chronicity, biopsychosocial characteristics of disease, disease burden, provider roles and collaborative care are given consideration. Strategies that may result in improvements in health outcomes of persons with SCD have been identified for use by the communities of interest including the providers, researchers, and health systems.

The purpose of the first manuscript was to present the findings of an integrative review and to evaluate the use of pain and pain instruments in persons with SCD. The addition of the biopsychosocial-religiosity/spirituality (BPS-R/S) framework to the pain instruments allows for the holistic evaluation of persons using the pain instruments. The use of the framework in this manuscript converted it from a fact-based document of pain instruments to a manuscript that encourages future research. This research should examine instruments that measure the constructs of BPS-R/S and their relationship to pain control. Another study that might be developed from this review is one that measures the relationship of services provided by psychologists, social workers, and chaplains to patients' perceptions of comprehensive care.

The second manuscript reports the results of a review of genetics and genomics literature designed to better understand genetic variability associated with single nucleotide polymorphisms and pharmacogenomics. The manuscript was written to respond to literature and personal reports of poor pain control and dissatisfaction with the health care experience in the emergency department (ED) by patients with sickle cell. Another important aspect were provider reports of difficulty in managing patients with SCD who seek pain control during vaso-occlusive crises. Two questions guided this review. Can the complexities of pain control be associated with pharmacokinetics (what the patient's body was doing with the medication)? Might genetic testing be used to identify single nucleotide polymorphisms as factors in the lack of pain relief with traditional therapeutic agents for persons with SCD? Training received at the National Institute of Health - Summer Genetics Institute provided the foundations to support the development of the manuscript.

The Diffusion of Innovation framework provided a substantive and tested guide for the introduction of the 'newer technology'. Genetic testing is not widely utilized to determine a person's genetic variability for prescriptive use, but this testing has substantively increased in the past 3-4 years. When the first draft of this manuscript was written, few certified labs were advertising genetic testing for single nucleotide polymorphisms; however, by the time of this document's completion, numerous laboratories were advertising directly to consumers and primary care providers. Additionally, government subsidized research has increased in the study of the 'omics' resulting in an enormous amount of data for analysis. In 2015, President Obama authorized a program entitled the Precision Medicine Initiative (PMI) with the purpose of utilizing an individual's genetic and other health information to personalize healthcare.

Genetics and genomics can be integrated into nursing practice to provide patient advocacy, patient education, to advance human science in this technologically evolving society.

For the ED/bedside nurse hearing a patient say that their pain is not relieved, or having a hypermetabolic patient slip into a coma-like state from a standardized dose of medication, genomics might provide an explanation. Once there is a better understanding, practice changes may occur. The changes may include policy and protocol development which may be used to address the various metabolic states of patients related to their genomic profiles.

The third manuscript reports findings from a secondary analysis of a large dataset from a sample of research participants with SCD. Dr. Coretta M. Jenerette collected the original data and tested the Theory of Self-Care Management for Vulnerable Populations and published the findings in her dissertation and subsequent publications. This theory has evolved into The Theory of Self-Care Management for Sickle Cell Disease. This dataset provided an opportunity to investigate concerns about the need for evidence-based clinical guidelines inclusive of the mental health needs in the sample. The results of the secondary analysis demonstrated relationships between psychosocial factors and quality of life. Depression negatively correlated to quality of life and proved to be the single most influential factor upon quality of life. The final analysis of the model containing all of the psychosocial factors explained 39.3 % of the variance in quality of life. The inference can be drawn that mental health matters to quality of life. The findings in this study will be used as groundwork for future research.

Limitations

A limitation in the development of the integrative review was the criteria that studies contained participants who were experiencing a vaso-occlusive crisis. A low number of emergent care manuscripts resulted in the use of non-emergent (clinic) measures being included.

In addition, studies were limited to those produced in the United States. A limitation of the literature review was the use of a limited number of databases and search terms. The inclusion of terms of additional single nucleotide polymorphisms found in persons with SCD might have strengthened the evidence for genetic testing. Limitations of the secondary analysis were associated with the general nature of using an existing dataset and the models used did not explain 60.7% of the variability.

Future Steps

The information in the manuscripts of this dissertation compendium provides a foundation for future research and may be used to improve the health outcomes of persons with SCD. There is a bulleted list of potential research ideas that came from the development of the three manuscripts attached in Appendix C.

Dialogues with persons with sickle cell disease and their family members continue to be illuminating and inspiring. Conversations with mentors, attendance at conferences, and the SCD Champion Series has facilitated the forging of connections to the community of sickle cell providers and researchers. A diverse body of scientific information was garnered through the examination of the pathology of SCD, research addressing biological, psychological, sociological, and spiritual issues; genomic and genetic testing, pharmacogenomics and the potential impact of precision medicine; analysis of a dataset that explored a rich amount of psychosocial information pertaining to the lives of persons with SCD. The literature used to develop the three manuscripts combined to create a diverse body of scientific evidence. This evidence has coalesced into foundational resources for moving forward in my roles as a researcher, sickle cell patient advocate, and nurse educator. Future work includes collaborating with hematologists and nursing colleagues to conduct community-based research with sickle cell

patients to determine barriers to care, provide patient and family education, and to identify what the families need to promote their health, self-efficacy, and quality of life.

Contribution to Nursing Science

Nursing as a science explores the human experience through human-to-human interactions. When nurses observe a problem, questions are generated and hypotheses are constructed. The hypotheses are tested through analysis and experimental processes. The experimentation process is scrutinized for errors before presenting the findings to colleagues and the community. The creation and presentation of this dissertation are steps toward contributing to nursing science. The studies in this dissertation were developed in response to seeing human suffering in persons with SCD and making an attempt to find ways to ameliorate the suffering through inquiry and the study of the existing evidence. Biopsychosocial-religiosity/spirituality domains are valuable in contributing to humanistic care and may benefit persons with SCD. There are many opportunities for study, research, and innovation using the emerging sciences to address this global health issue.

Appendix A: Glossary of Genetics Content in Chapter 3

Interindividual variability, “The interindividual variability in the response to any drug can be defined as "an effect of varying intensity occurring in different individuals at a specified dose of a drug", or as "a requirement of a range of concentrations (doses) in order to produce an effect of specified intensity in all of the patients" (Rocca, Dragani, & Pagliaccia, 2013, p.1).

Pharmacokinetics (PK), “includes compliance, absorption, bioavailability, distribution, biotransformation” (Rocca, Dragani, & Pagliaccia, 2013, p.1).

Pharmacodynamics (PD), “comprising the status of drug target, resistance, tolerance; environment, for example interaction with xenobiotics (drugs, hormones and habits)” (Rocca, Dragani, & Pagliaccia, 2013, p.1). (Buxton, 2005, p.1).

Pleiotropic, “multiple, often seemingly unrelated, physical effects caused by a single altered gene or pair of altered genes having multiple phenotypic expressions” (U.S National Library of Medicine, 2015, n.p.).

References: Glossary of Genetics Content

- Rocca, B. Dragani, A. & Pagliaccia, F. (2013). Identifying determinants of variability to tailor aspirin therapy. *Expert Review of Cardiovascular Therapy*, 11 (3), 365-379. Retrieved from http://www.medscape.com/viewarticle/780701_2.
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Appendix B: IRB - Health Sciences South Carolina: A collaborative to advance health sciences

Current State

Not Human Subjects Research

[View Study](#)

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[Log Public Comment](#)

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History | [Personnel](#) | [Attachments](#) | [Reviewer Notes](#)

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Coor	Not Human Subjects Research	Cooper, CIP, Linda	5/18/2015 2:55 PM
	The IRB has determined that this research project meets the criteria for 'Not Human Subjects' research.		
Dept	Departmental Approval Issued	Acierno, Ronald E.	5/11/2015 10:25 AM
Ment	Mentor Approval Issued	Stuart, Gail Wiscarz	5/11/2015 5:46 AM
PI	Study Submitted for Review	Vick, Lori L	5/7/2015 11:10 PM
SS	Edit Guest Access	Vick, Lori L	5/7/2015 10:51 PM
SS	Edit Guest Access	Vick, Lori L	5/6/2015 7:02 PM
i	Created Study	Vick, Lori L	5/6/2015 8:44 AM
🔄	Study Modified - Major Version	Vick, Lori L	5/6/2015 8:44 AM

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Appendix C: Future research ideas and topics

Physiological

- Diagnostic tests to measure the extent, severity, and location of tissue damage during vaso-occlusion.
- Analyzing the spectrin (the fibers that create RBC flexibility) in normal versus sickled cells to determine differences
- Find out the chemical and genetic influences that stimulant spectrin
- What can be done at a genetic level to prevent the abnormal folding of RBCs? Explore lentivirus research (LVR)
- Post bone marrow transplantation; (1 year, 2 years, 5 years, 10 years---long term study)

Biopsychosocial

- New research question: Is there a significant difference in pain control when primary providers in emergency departments collaborate with psychologists, social workers, and chaplaincy team members when they encounter a patient with SCD? (Integrative review)
- What are prevention strategies for transition-associated deaths in patients with sickle cell disease? (from Dr. Jenerette's research)
- What is the impact of improving the communication skills of the individual with SCD? (from Dr. Jenerette's research)
- Examine the coded data available to determine how many providers have given patients with SCD a diagnosis of depression during a clinic visit, admission to hospital and compare that with psychotropic medication prescriptions written and filled. (Discussion w/ Dr. Tanabe) Check for Referrals for psychotherapeutic interventions e.g. counseling, Cognitive Behavioral Therapy, psychotherapy, support group, etc.

- Define the sequelae associated with the neurological changes associated with persistent pain and enhanced sensitivity to pain and determine measures to intervene and manage these manifestations (per Dr. Ballas's research).

Community-based

- What is the relationship between persons with SCD attending support groups and self-efficacy?
- What is the role of the community church in the health management of members with SCD?
- What data needs to be collected to create interventions that will be considered to have promoted culturally meaningful and comprehensive care?