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The Multidimensional Characteristics of Persistent Pain in Adults with Sickle Cell Disease

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The Multidimensional Characteristics of Persistent Pain in Adults with Sickle Cell Disease

by

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DISSERTATION

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This dissertation includes reprints of material published in the Journal of Pain Management Nursing and the Journal of Pain and Symptom Management. The conceptual model of the "Biopsychosocial-Spiritual Model of Chronic Pain in Adults with Sickle Cell Disease" published in 2011 in the Journal of Pain Management Nursing is part of an article that is comparable to the theoretical framework section of a standard dissertation. The first article in this dissertation, published in 2010 in the Journal of Pain and Symptom Management "A Review of the Literature on the Multiple Dimensions of Chronic Pain in Adults with Sickle Cell Disease" is comparable to the Literature review section of a standard dissertation. The second article, "Occurrence and Characteristics of Persistent Pain in Adult Outpatients with Sickle Cell Disease" has been submitted for

publication to the Journal of Pain and is comparable to a portion of the Methods and Results sections of a standard dissertation. The third and final article "Pain Catastrophizing, Religiosity/Spirituality, and Quality of Life in Adults with Persistent Sickle Cell Pain" is being prepared for submission to the Clinical Journal of Pain and is included as the second portion of the Methods and Results sections of a standard dissertation. Ms. Taylor contributed 90% of the work to these articles and serves as first author on each paper, her dissertation committee members are listed as co-authors and all members actively participated in the work.

Dedication

With humble gratitude, first and foremost I give all praise, honor, glory, and thanks to God. Truly, I never would have made it without You Lord. Through those times when the road was rough, and the tides, were high, when I wiped back tears because I wanted to cry, You kept me strong, You kept me fierce, and You kept me standing. You helped me to weather the many storms that came my way; You carried me over every bridge. You helped me to climb this mountain and brought me from the lowest valley to the mountaintop. I love You Lord and I hope I serve You well on this journey.

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Abstract

The Multidimensional Characteristics of Persistent Pain in Adults with Sickle Cell Disease

Lou Ella V. Taylor

Sickle cell disease (SCD) is a major healthcare and societal problem that affects millions of people worldwide. Sickle cell pain is the hallmark feature of SCD and includes manageable and unmanageable persistent pain that affects every aspect of an individual's life. Most of the research on pain in SCD has focused on children with acute vaso-occlusive episodes. Consequently, significant gaps exist in our knowledge of the occurrence and characteristics of manageable and unmanageable persistent pain in adults with SCD.

The specific aims of this study in a sample of adults with SCD were to: 1) determine the occurrence of persistent SCD pain and compare those with manageable and unmanageable persistent SCD pain on demographic and clinical characteristics, as well as, pain-related measures; 2) compare those with manageable and unmanageable persistent SCD pain on coping strategies; and 3) determine which factors influence quality of life (QOL) in these patients.

One hundred and three patients who were ≥18 years with SCD completed questionnaires on demographic, clinical, and pain characteristics, as well as, the Pain Catastrophizing Scale (PCS), the Duke Religious Index (DRI), and the Medical Outcomes Study Short-Form (SF-36). Patients were divided into those with manageable (average pain intensity ≤5) and unmanageable pain (average pain intensity >5) based on established cutpoints. Final analyses were done on 94 patients.

Seventy percent of patients had manageable pain and 30% had unmanageable pain. Patients with unmanageable pain reported higher ratings for all of the items on the Pain Quality Assessment Scale (PQAS); were more likely to be taking only a short-acting opioid; reported less relief from analgesic medications, and reported significantly lower SF-36 scores. Significant negative correlations were found between pain catastrophizing and religiosity/spirituality, and physical and mental health. Several variables were found to have an influence on QOL. These findings suggest that persistent pain in adults with SCD is a significant problem. More research needs to evaluate how adults with SCD cope with persistent pain and its impact on their QOL.

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Chapter 1

Introduction

Sickle cell disease (SCD) is the most common genetic blood disorder that is complicated by acute and persistent pain.[32,33,48] In fact, pain associated with SCD is the most common reason that patients seek treatment.[32,33] In 2004, the costs associated with hospitalizations related to SCD were estimated at approximately $500 million.[40] The majority of these costs were for painful vaso-occlusive episodes (VOEs). Of note, acute recurrent VOEs are associated with increased morbidity and mortality in adults with SCD.[32,33] Sickle cell pain can begin as early as 6 months of age in the form of acute VOEs.[9,33] These VOEs can last throughout the person's life and evolve into persistent pain (i.e., pain≥3 months).[37,38] However, persistent SCD pain can occur as a result of other causes (e.g., avascular necrosis, treatment related to SCD).

Sickle cell pain can be due to nociceptive, neuropathic, or inflammatory mechanisms.[3,28] Nociceptive pain (e.g., acute or recurrent VOEs, pain associated with leg ulcers)[3,28] can be somatic or visceral. This type of pain occurs when peripheral nociceptors are activated as a result of damage to the vascular surrounding endothelium and tissues as a result of deoxygenated hemoglobin, which distorts the shape of and damages red blood cells (RBCs). Whereas, nociceptive SCD pain is due to actual tissue damage, neuropathic SCD pain is caused by abnormal somatosensory processing in the peripheral or central nervous system and may occur in the presence (i.e.,VOEs)[3,28] or absence (e.g., hyperalgesia secondary to opioid withdrawal)[7] of obvious central or peripheral nerve injury.[3,30] In addition, sickle cell pain may occur due to secondary inflammatory responses caused by a destructive cycle of recurrent infarctive tissue

damage.[29] Patients with persistent SCD pain can experience all three pain mechanisms simultaneously. These mechanisms; the chronicity of SCD pain; and the mortality associated with recurrent acute VOEs distinguish persistent SCD pain from other persistent pain conditions and renders it a unique pain syndrome.

Persistent SCD pain is not only complex, but multidimensional as well, involving biological,[36] psychological,[2] sociological,[2] and spiritual factors.[8,14] Biological factors include comorbid conditions, age, and gender. Psychological factors include active coping (e.g., ignoring pain sensations, calming self-statements); passive adherence coping (e.g., resting, taking fluids); and affective coping (e.g., catastrophizing, praying, hoping, isolation). Sociological factors include social support and socioeconomic status. Spiritual factors intersect with religious coping factors and include belief in the Divine (i.e., God), church attendance, and praying.

Persistent pain has a negative impact on the QOL of adults with SCD.[4] In one study,[4] patients with persistent pain from SCD reported worse QOL compared to other persistent pain conditions in four of the eight subscales of the SF-36 (i.e., role-physical functioning, social functioning (SF), health perceptions (HP), bodily pain (BP). Persistent pain in adults with SCD had the greatest impact on physical functioning. Other studies that reported on the association between pain and QOL in adults with SCD focused on recurrent VOEs[41] or did not identify what type of pain was evaluated.[24,47] Consequently, little is known about the impact of persistent SCD pain on QOL.

Several biological,[22,44] psychological,[12,34] sociological,[1,13] and religious/spiritual factors,[20] as well as, pain severity[21,35,45] have been identified as predictors of QOL in patients with other persistent pain conditions, (e.g., cancer pain, chronic osteoarthritis,

chronic wound pain). However, little is known about how these factors influence QOL in adults with persistent SCD pain. More studies are needed to address the gaps in knowledge about the associations among persistent SCD pain and demographic, clinical, and biopsychosocial-spiritual factors in adults with SCD.

The theoretical framework that guided this research was based on the Biopsychosocial-Spiritual Model for Chronic Pain in Adults with SCD developed by Taylor and colleagues (Figure 1).[43] This model addresses the multidimensional nature of persistent pain in adults with SCD. A disease-specific model of persistent SCD pain has utility in pain management and offers directions for future research.

Since the discovery of SCD over 100 years ago,[15] due to advances in clinical care, research, and health policies, patients are living well past their teens and into late adulthood.[26,36] Despite these advances in the legal, scientific, and health-related domains of SCD, most of the research has focused on acute sickle cell pain in children.[16-18] Consequently, little is known about the occurrence and characteristics of persistent pain in adults with SCD. In a review of the literature on chronic pain in adults with SCD,[42] the occurrence of persistent pain ranged from 29% to 100%. However, many of the studies included children and focused on VOEs. These same limitations were found in studies of the characteristics of persistent pain in these adults.[2,10,38]

Consistent with other persistent pain conditions,[27,45] the intensity of persistent SCD pain can range from mild to moderate and severe.[4,39,46] Previous research in oncology patients with persistent cancer pain found significant differences in the pain experience of those with mild and moderate to severe pain.[45] Zelman and colleagues[50,51] introduced the concept of "manageable pain" (i.e., average daily pain ≤5) in patients with

a variety of chronic pain conditions. However, no studies have evaluated for differences in pain characteristics in patients who experience manageable versus unmanageable persistent SCD pain. Given that previous research found that patients with persistent SCD pain experience moderate to severe pain that is not well managed[11,23,31] and unrelieved,[5] more studies are needed to identify differences in pain characteristics in patients with manageable versus unmanageable persistent SCD pain.

Due to the multidimensional nature of persistent SCD pain, a variety of coping strategies are needed to manage this unique pain. Although previous studies have reported on psychological coping strategies in adults with persistent SCD pain,[2,6,8,14,19,25] few studies have reported on coping strategies associated with the biological,[36] spiritual,[8,14] and sociological[2] dimensions of persistent SCD pain. Given the lack of research on the multidimensional characteristics of persistent pain in adults with SCD, the purposes of this dissertation study in a sample of adult outpatients with SCD were to: determine the occurrence and characteristics of persistent SCD pain; evaluate for differences in demographic, clinical, and pain characteristics between those with manageable and unmanageable persistent SCD pain; evaluate for differences in pain catastrophizing, religiosity/spirtituality, and QOL between the two pain groups; and evaluate the effects of selected demographic, clinical, and pain characteristics, as well as, biopsychosocial-spiritual characteristics on the QOL of adults with persistent SCD pain.

Chapter two of this dissertation entitled: *A Review of the Literature on the Multiple Dimensions of Chronic Pain in Adults with Sickle Cell Disease*,[42] provides a comprehensive review of the multidimensional characteristics of persistent pain in these adults. Identifying gaps in the literature on persistent SCD pain can help to guide future

research. Furthermore, an understanding of the multiple dimensions of persistent pain in adults with SCD is needed to understand the problem, guide treatment, and improve outcomes for this population.

Chapter three is entitled: *Occurrence and Characteristics of Persistent Pain in Adult Outpatients with Sickle Cell Disease*. An understanding of the occurrence and characteristics of persistent SCD pain is needed to demonstrate the impact of this problem in adults with SCD. The purposes of this study were to investigate the occurrence and multidimensional characteristics of persistent pain in adult outpatients with SCD and compare patients with manageable and unmanageable pain on a number of demographic and clinical characteristics and a variety of pain measures.

Chapter four is entitled: *Pain Catastrophizing, Religiosity/Spirituality, and Quality of Life in Adults with Persistent Sickle Cell Pain*. Patients with persistent SCD pain utilize maladaptive and adaptive coping strategies. Both coping strategies, along with other factors (e.g., demographic and clinical characteristics) can influence QOL in these adults. The purposes of this study were to compare adults with manageable and unmanageable persistent SCD pain in catastrophizing, religiosity/spirtituality, and QOL and determine the influence of demographic, clinical, and pain characteristics, as well as, biopsychosocial-spiritual factors on the QOL of these adults.

After approval by the Committee on Human Research at the University of California, San Francisco (UCSF) and the Institutional Review Board at Children's Hospital and Research Center, Oakland (CHRCO), informed consent was obtained from each patient. Adult outpatients with SCD who were at least 18 years of age were recruited through a variety of methods to participate in this study. Due to the high occurrence of

persistent SCD pain in this sample, based on the work of Zelman and colleagues,[49,50] ratings of average pain were used to categorize patients into those with manageable (≤5=mild pain, n=66) or unmanageable (>5=moderate to severe, n=28) pain. Of these 94 patients, 70% had manageable pain and 30% had unmanageable pain. Patients with unmanageable pain reported higher ratings for all of the items on the Pain Quality Assessment Scale (PQAS); were more likely to be taking only a short-acting opioid; reported less relief from analgesic medications, and reported significantly lower SF-36 scores. Significant correlations were found between demographic and clinical characteristics, as well as, catastrophizing and QOL. In addition, several of these factors had an influence on QOL in these adults.

Chapter five is the final chapter of this dissertation. This chapter discusses the conclusions, implications for clinical practice, and recommendations for future research.

Appendix

Figure 1. Conceptual model of the Biopsychosocial-Spiritual Model of Chronic Pain in Adults with Sickle Cell Disease.

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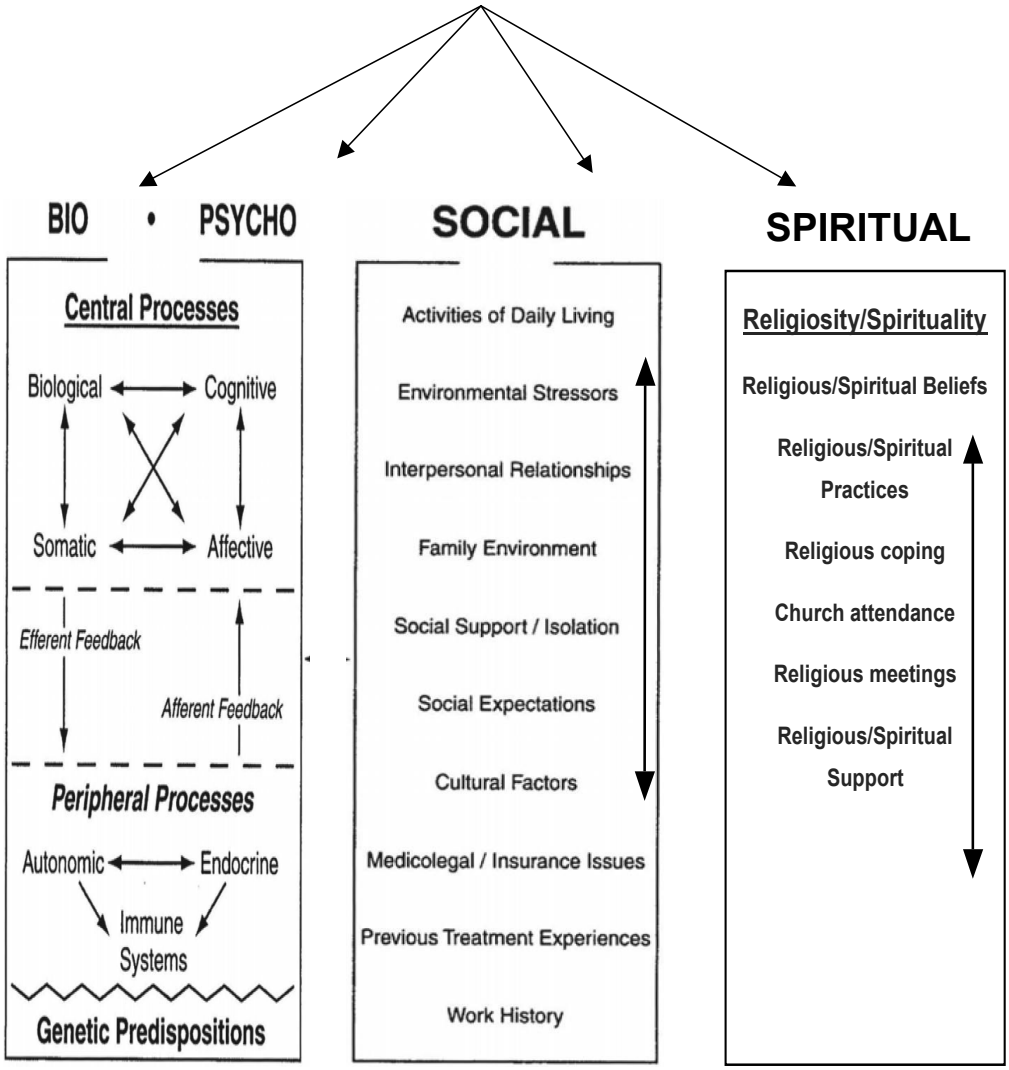

Figure 1. A conceptual model of the Biopsychosocial-Spiritual Model of Chronic Pain in Adults with Sickle Cell Disease by L.V. Taylor. Copyright © 2010. Adapted from A conceptual model of the biopsychosocial interactive processes involved in health and illness. From "Comorbidity of Chronic Pain and Mental Health Disorders: The Biopsychosocial Perspective," by R. J. Gatchel, *American Psychologist, 59*(8)*,* 795–805. Copyright © 2004 by the American

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Chapter 2.

A Review of the Literature on the Multiple Dimensions of Chronic Pain in Adults with Sickle Cell Disease.

Taylor LE, Stotts NA, Humphreys J, Treadwell MJ, Miaskowski C. A review of the literature on the multiple dimensions of chronic pain in adults with sickle cell disease (2010). *J Pain Symptom Manage.* 40:416-435, 2010

Abstract

Sickle cell disease (SCD) is a major healthcare and societal problem that affects millions of people worldwide. In Nigeria, 45,000 to 90,000 babies are born each year with SCD. In the United States, SCD is the most common genetic disorder, affecting more than 80,000 people, the majority of whom are African American. Sickle cell pain is the hallmark feature of SCD. Most of the research on pain from SCD has focused on children with acute pain associated with sickle cell crisis. Consequently, very little is known about the occurrence and characteristics of chronic pain, especially in adults with SCD. Individuals with SCD who experience chronic pain are often underserved and their pain is under-treated. This under-treatment may result in millions of dollars per year spent on emergency room visits, hospitalizations, and lost work productivity. The primary purpose of this literature review was to summarize the findings from studies that evaluated the characteristics of chronic pain in adults with SCD. Each of the studies included in this review was evaluated to determine if it provided data on the following multidimensional characteristics of chronic pain: occurrence, number of pain episodes, duration, pattern, quality, location, intensity, aggravating factors, relieving factors, and impact of pain on function. A secondary purpose was to identify gaps in knowledge and directions for future research on the multiple dimensions of chronic pain in adults with SCD.

Keywords

Sickle cell disease; sickle cell pain; sickle cell crisis; chronic pain; multidimensional; adults

Introduction

Sickle cell disease (SCD) is a major healthcare and societal problem that affects millions of people worldwide (1). In Nigeria, which has the highest incidence of SCD worldwide, 45,000 to 90,000 babies are born each year with SCD (2). In the United States (US), SCD is the most common genetic disorder; more than 80,000 people are affected, the majority of whom are African American (3). This U.S. prevalence of SCD is likely to be a low estimate because no national registry for SCD exists and statistics are mainly provided for sickle cell anemia, which is the homozygous form of SCD (4). During the years 1979 to 1995, the age adjusted mortality rates for SCD ranged from 0.2 deaths to 14.6 deaths per 1 million persons (5). In 2004, 699 adults with SCD died while hospitalized (6).

Sickle cell pain (SCP) is the hallmark feature of SCD and a measure of its clinical severity (7). Of note, the mortality rate for SCD has been linked to the frequency of sickle cell pain episodes. In one study (8), patients with SCD who were over 20 years of age and experienced more than three pain episodes per year were approximately two times more likely to die earlier than those who had less frequent pain episodes.

In 2004, 83,149 adults were hospitalized in the U.S. for SCD, incurring approximately $488 million in associated costs (6). These figures have increased since 1997, when approximately 75,000 hospitalizations per year for children and adults with SCD yielded a total cost of $475 million (7). One study (9) found a savings of $ 1.7 million over a five-year period when patients with uncomplicated painful crises from SCD avoided hospitalization through treatment in a day hospital designed specifically for this population. Most hospitalizations of patients with SCD are for a pain crisis. Another

study (10) observed that the number of pain episodes was significantly associated *(P* < 0.001) with the patients' use of hospital services, even more so than demographic and clinical variables (i.e., co-morbidities, hemoglobin level). A lifetime of unpredictable, recurrent, intense, and frequently persistent pain experiences and the accompanying recurrent use of opioids, make pain associated with SCD unique among pain syndromes (11).

Until the mid 1970s, individuals with SCD did not live past their teens (12). However, due to advances in treatment, the life expectancy of individuals with SCD has tripled from 14 years in 1973 to the current median survival of 42 years for women and 48 years for men (12,13). Because increased survival is a relatively recent event, most of the research on pain has focused on children with acute, severe pain associated with a sickle cell crisis. Consequently, very little is known about the occurrence and characteristics of chronic pain, especially in adults with SCD. As with children, the majority of studies on pain in adults with SCD has focused on acute pain. In a review of the literature on the pharmacologic management of pain associated with SCD (14), no studies were found that focused on chronic pain.

The limited information available indicates that individuals with SCD who experience chronic pain are often underserved and their pain is under-treated. This under-treatment may result in increased healthcare costs associated with emergency room visits, hospitalizations, and lost work productivity. The primary purpose of this literature review was to summarize the findings from studies that evaluated the characteristics of chronic pain in adults with SCD. Since chronic pain is a multidimensional experience, each of the studies included in this review was evaluated to determine if it provided data on the

following characteristics of chronic pain: occurrence, number of pain episodes, duration, pattern, quality, location, intensity, aggravating factors, relieving factors, and impact of pain on function. A secondary purpose was to identify gaps in knowledge and directions for future research on the multiple dimensions of chronic pain in adults with SCD. A multidimensional analysis of chronic pain in adults with SCD is required to more fully understand the nature of the problem and to improve pain assessment and treatment in this population.

Methods

A search of the PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO databases was conducted for all research that evaluated the multiple dimensions of the chronic pain experience of adults (i.e., those 18 years or older) with SCD. The searches were limited to the years 1972 to 2009 because most research on SCD did not take place until after the National Sickle Cell Anemia Control Act was signed into law in 1972 (15). Criteria for study inclusion were: adults with SCD and chronic pain; studies that reported on at least one of the 10 pre-specified dimensions of chronic pain; and research published in English. The determination of chronic pain was based on pain associated with a chronic disorder (e.g., avascular necrosis, chronic bone pain, degenerative disease of the spine) or the definition of chronic pain established by the International Association for the Study of Pain (16), which is pain that persists or recurs for more than three months. Studies were excluded if they evaluated SCP only in children and/or evaluated acute pain unrelated to SCD. Based on this initial screening and a careful review of the reference lists from these studies, 19 studies met the inclusion criteria for this review (8,10,17-33).

This literature review provides a summary of the design and methods used in these studies, as well as a summary of the pain dimensions evaluated across these 19 studies of chronic pain in adults with SCD. To summarize the data from the studies, a number of tables were generated that address each dimension of chronic pain in adults with SCD. In addition, to summarize information on a variety of characteristics, weighted means and proportions for a number of demographic characteristics and dimensions of chronic pain were calculated across those studies that provided information. Table 1 summarizes the multidimensional characteristics of chronic pain in adults with SCD that were evaluated across the 19 studies. Table 2 provides a detailed summary of each study. Table 3 summarizes the percentage of participants with chronic pain identified in each study and identified which studies included patients with acute, recurrent sickle cell crisis pain, and mixed pain. Table 4 summarizes the words used by participants to describe their pain. Table 5 summarizes common sites of chronic pain in adults with SCD. Table 6 summarizes the strategies used by participants to manage their pain. All of the studies in this literature review provided information on more than one dimension of chronic pain in adults with SCD.

Summary of the Design and Methods Used in Studies of Chronic Pain in Adults with SCD

Seven cross sectional studies (10,18,19,23,25,29,31) and 12 longitudinal studies (8,17,20-22,24,26-28,30,32,33) have investigated chronic pain in adults with SCD. Three studies evaluated interventions for pain (18,31,33). Only one study used qualitative methods (19).

The sample sizes in these studies ranged from 1 to 3578 (total number of participants = 5234). Nine studies (47%) had samples of less than 50 (Table 1). Two of them were case studies of patients with chronic pain caused by avascular necrosis of the hips and shoulder (30,32).

All 19 studies provided some information on the demographic characteristics of the participants. However, only nine (47%) provided details on socioeconomic status. Approximately half of the studies (47%) included both children and adults (8,18,20-23,27,30,32). Across the 19 studies, slightly more females participated than males (females = 2761, 53%; males = 2473, 47%). The adults ranged from 18 years to 71 years (mean age = 32.6 years). An attempt was made to calculate the percentage of adults who reported on particular demographic characteristics (i.e. educational level, employment, marital status, hemoglobin type), but due to the inclusion of children in some of the studies and data reported inconsistently, calculations of weighted means/proportions were done for those studies with only adult participants.

In three of the 19 studies (24,25,28), approximately 82% of the participants were high school graduates, had some college, or a college degree. Approximately 17% of the participants had not completed high school. In the four studies that reported on employment (17,19,24,25), most of the participants (61%) were unemployed and/or disabled. In four of the 19 studies that reported on marital status (10,19,24,25), 72% of the participants were unmarried or separated. Only two studies (8,32) reported on the annual income of the participants. In one study (8), 57% of the participants reported an annual income of < $10,000. In the second study (32), 39% of the participants reported an annual income of < $10,000. In four studies (10,24,26,28), approximately 63% of the

participants had hemoglobin (Hb) type SS (the most common genotype in SCD, and along with Hb Sβ° thalassemia, the more severe form of the disease), approximately 29% had Hb SC (the second most common genotype in SCD), and 8% had Hb Sβ ($S\beta^{+}$ thalassemia or Sβ° thalassemia).

Six studies (10,17,19,24,25,33) reported on the race/ethnicity of the participants. In four of these studies (17,24,25,33), approximately 96% of study participants were African American and/or Black. In three studies (24,25,33), all of the participants were African American. In one study (10), all of the participants were African and Caribbean. In another study (19), participants were African, Afro-Caribbean, and Portuguese.

Several instruments were used to measure chronic pain and quality of life (QOL). In eight studies (17,20-22,24,27,28,32), daily pain diaries obtained information on the presence or absence of sickle and non-sickle related pain, pain intensity, pain location, pain descriptors, precipitants of sickle pain, pain relieving techniques, actual or potential stressors, healthcare use, and limitations in physical and social activities. One study (25) used the McGill Pain Questionnaire. In another study (29), the Multidimensional Pain Inventory (MPI-2), a short form of the West Haven-Yale Multidimensional Pain Inventory (WHYMPI), was used to assess pain. Six studies used a visual analog scale (VAS) to assess pain intensity (20,22-25,31). Four studies (10,17,27,28) used the Medical Outcome Study 36-item Short Form (SF-36) to measure bodily pain and QOL. Pain interviews were done in three studies (10,19,24). Two studies did not report which instruments were used to measure pain (26,33). Validity and reliability of all of the instruments were reported or referenced.

Fourteen of the 19 studies listed exclusion criteria. In three studies (25,29,32), participants were excluded if they were having a pain crisis or other urgent medical conditions at the time of the clinic visit. In three studies (10,22,32), participants who could not read, write, and comprehend English were excluded. In two studies (21,22), participants were excluded if they received chronic transfusions or hydroxyurea. The main reason participants refused to participate or withdrew from these studies was time constraints.

In terms of the types of chronic pain that were evaluated, five studies (18,23,26,29,30) analyzed a number of dimensions of chronic pain in adults with SCD. Six studies (8,10,19,22,23,25) analyzed recurring episodes of acute pain crises, a common cause of chronic pain in adults with SCD. Nine studies (17,20,21,24,27,28,31-33) included participants with multiple types of pain (e.g., acute pain superimposed on chronic pain). The majority of the studies that evaluated multiple types of pain did not provide detailed information on the specific etiology of the chronic pain.

None of the studies in this review defined chronic pain. However, three studies provided a definition for SCP (20,22,23). In two studies (20,22), this was defined as vaso-occlusive episodes typically experienced by patients with SCD. In another study (23), SCP was defined as acute and chronic pain that varied in intensity, location, quality, and temporal pattern. Three studies (21,28,32) defined sickle crises. In one study (21), sickle cell crisis was defined as an unpredictable recurrent episode of pain from vaso-occlusion. In another study (28), crises were referred to as acute episodes of ischemic pain thought to be due to vaso-occlusion. In another study (32), crises were self-defined by each patient.

Across these 19 studies, pain was often used interchangeably with sickle cell pain, which made it difficult to distinguish whether the pain experience was caused by chronic pain, a vaso- occlusive episode, mixed pain, or pain unrelated to SCD. When pain was measured, it was not clear whether SCD pain versus pain unrelated to SCD was measured. In addition, no consistent definition for a pain episode was used across all seven studies that provided a definition. In some studies, an episode of pain was defined broadly, while in others it was defined as an acute pain crisis (20-24,27,32). Only three studies (20,24,32) differentiated SCD pain from other types of pain, but it was not clear whether the SCD pain or other pain was acute or chronic. Also, it was not clear whether SCD pain versus pain unrelated to SCD was measured.

Summary of the Pain Dimensions Evaluated Across Studies of Chronic Pain in Adults with SCD

Chronic pain in SCD can be due to many factors. The most common causes are recurrent pain episodes due to vaso-occlusion of the microcirculation and destruction of bones, joints, and visceral organs (11). Chronic pain in adults with SCD is a multifaceted experience that involves sensations, emotions, cognitions, memories, and context. Therefore, chronic pain must be assessed and managed from a multidimensional perspective (11,34).

Pain Occurrence

Pain occurrence refers to the frequency with which an individual experiences pain in a given period of time or the incidence of a particular type of pain in a given population. Both of these definitions are needed to characterize the magnitude of the chronic pain experience of adults with SCD.

In the 11 studies that reported on pain occurrence (8,17,18,20,24,26,28,30-33), participants reported experiencing chronic pain on 13% to 50% of study days. The percentage of participants with chronic pain varied from 29% to 100% across seven studies with a weighted mean of 65% (18,26,29,30-33).

Pain Episodes

Chronic pain in adults with SCD can include superimposed acute sickle cell pain with accompanying vaso-occlusive episodes/pain crisis, and/or pain of multiple etiologies. A painful episode, which is caused by ischemic tissue injury that results from occlusion of the micro-circulation by sickled red blood cells, is the most common symptom of SCD. Furthermore, the frequent episodes of acute pain in SCD can resemble chronic pain (11).

The number of vaso-occlusive episodes was reported in nine studies (8,10,17,21,22,28,31-33). The majority of the participants had at least one painful vaso-occlusive episode per year, with some participants having as many as 24 vaso-occlusive episodes per year. The weighted mean number of vaso-occlusive painful episodes across the nine studies was 1.3 annually.

Duration

Six studies (10,18,20,22,24,28) assessed the duration of pain in adults with acute sickle cell pain crisis and/or multiple pains from SCD. The mean duration of pain was variable, ranging from 10.1 hours to 9.6 days. Women reported pain episodes of longer duration than men. Increased fetal hemoglobin levels were associated with longer duration between pain episodes (22).

Pattern

For treatment purposes, it is important to determine the regularity of chronic pain and whether or not the pain is worse at a particular time of the day or night. Seven studies reported on the pattern of pain in adults with SCD (19,20,22,23,26,30,33). In three studies (19,22,23), the pain came on rapidly/suddenly and unexpectedly. These data are consistent with previous studies on the pattern of pain in acute sickle cell vaso-occlusive episodes (11,35).

Quality

In the four studies that reported on pain qualities (19,20,23,30), 28 pain descriptors were listed (Table 4). Some of the most commonly used words to describe pain were: awful, comes on all of a sudden, comes on slowly, severe, steady, uncomfortable, unbearable, and vague.

Location

In the nine studies that reported on the location of chronic pain in adults with SCD (18-20, 22,23,26,30,31,33), the hips were the most common pain site, followed by the back (Table 5). The percentage of participants with hip pain ranged from 60% to 100% (weighted mean = 81%) (18,26,30,33). The percentage of participants with back pain ranged from 23% to 99% (weighted mean = 60%) (18,23,30). The percentage of participants with pain in multiple bones and/or areas simultaneously ranged from 5% to 100% (weighted mean = 14%) (18,19,23,30, 31,33). In two studies (22,23), females reported more painful sites than males.

Intensity

Pain intensity was measured in 12 studies (10,17,18,20,22-24,27-29,31,32). In eight studies (10,18,20,22,28,29,31,32), mean pain intensity scores ranged from

approximately 3.5 to 10 on a 0 to 10 VAS. The weighted mean across these eight studies was 5.3. In four studies (10,17, 24,27), the bodily pain score on the SF-36 ranged from 46.5 to 52 on a 0 to 100 scale. The weighted mean pain intensity score across these four studies was 48, which was significantly ($P < 0.0001$) lower than national norms and cohorts with other chronic pain conditions (i.e., hemodialysis, cystic fibrosis, asthma). In one study (31), mean pain intensity increased as the number of pain days increased. In three studies (23,31,32), females reported higher pain intensity scores than males. However, in another study (10), no differences in pain intensity scores were found between women and men.

Aggravating Factors

Six studies reported on the aggravating factors associated with chronic pain in adults with SCD (24,26,27,29-31). Stress, negative affect, physical exertion, exposure to extreme temperatures, and the number of sickle cell episodes were significantly associated with increased SCD pain. In one study (24), negative affect was higher on pain days (mean=7.9) compared to nonpain days (mean=3.6). In this study, higher levels of physical exertion were associated with higher levels of pain *(*$P < 0.001$) and increased stress was associated with increases in same day pain *(*$P < 0.001$). In another study (27), the percentage of days with sickle cell crisis was an independent predictor of bodily pain. As the proportion of days with crisis increased, so did pain.

Relieving Factors

Fourteen studies reported on factors that relieved chronic pain in persons with SCD (10,18-22,24-27,30-33). Overall, 23 pain management strategies were reported (Table 6). In ten studies (67%) (10,19-22,28,30-33), analgesic administration was the

most common strategy used to manage chronic pain. The majority of the patients used analgesics either alone or in combination with nonpharmacologic methods.

Seven studies reported on the use of nonpharmacologic measures for chronic pain in adults with SCD (10,18,19,20,21,25,33). Four studies reported on the use of prayer (10,20,21,25). In one study (18), participants reported significant decreases in pain intensity following massage (i.e., 9.6 ± 0.80 before massage and 2.8 ± 0.75 after massage). In another study (21), when analgesics were used along with nonpharmacologic measures, watching television or reading a book was the primary method of relieving pain, followed by talking with people. In a third study (25), participants who attended church one or more times per week reported lower overall pain intensity scores *(P* < 0.0004).

Functional Status

In the 11 studies that reported on the effects of chronic pain on the functional status of adults with SCD (10,17-20,24,25,27,29,30,31), chronic pain had significant negative effects on participants' QOL. In three studies (10,17,27), acute recurring vaso-occlusive episodes and mixed pain had a significant negative impact on participants' physical and social functioning. In another study (17), baseline daily pain intensity was a significant predictor of decrements in the following QOL outcomes: general health now, social functioning, role limitations due to physical and emotional health, mental health, energy, fatigue, pain recall, tension-anxiety, depression-dejection, and ladder of life (participants own rating of their QOL). In one study (24), participants with more severe pain had increased work absences. Participants in another study (19) had recurrent

themes of fear, death, uselessness, helplessness, loss of virility, and worsening ill health associated with increased pain.

Conclusions and Recommendations for Future Research

Because of advances in treatment, persons with SCD are living longer, which means that more adults are experiencing chronic pain associated with their disease. Findings from this review suggest that significant gaps exist in our knowledge of the multiple dimensions of chronic pain in this population. To date, no studies have examined in a comprehensive manner the multiple dimensions of the chronic pain experience of adults with SCD. A critique of the 19 studies done to date reveals some limitations.

First, studies that focused only on adults with SCD who experience chronic pain are extremely limited. Findings from this review suggest that chronic pain occurs in at least 29% of adults with SCD and most frequently in those 25 to 44 years of age. However, almost 50% of the studies reviewed included both children and adults, which makes it difficult to accurately assess the magnitude of the problem in adults. If children are included in studies of chronic pain in adults with SCD, and data are not reported separately for adults, one cannot determine the impact of chronic pain in adults. Studies are needed that focus specifically on adults with chronic pain from SCD.

Second, most of the studies on chronic pain in adults with SCD investigated recurring acute vaso-occlusive pain episodes and pain intensity related to these episodes. Only a few studies examined other dimensions of chronic pain or chronic pain due to other causes. Chronic pain in adults can occur from complications of SCD, such as

avascular necrosis, ankle ulcers, or acute pain superimposed on chronic pain. Studies are needed that examine the multiple causes of chronic pain in this population.

Third, only 47% of the studies provided details on both demographic characteristics and socioeconomic status. Some of these studies provided only partial details and income was evaluated in only two studies. Chronic pain in adults with SCD is a multi-factorial experience which negatively impacts many areas of the individual's QOL (e.g., family responsibilities, employment status). In order to better understand the association between demographic characteristics and socioeconomic status and chronic pain in adults with SCD, studies are needed which include more specific information on socioeconomic status.

Fourth, almost half of the studies in this review involved relatively small samples. Some of the potential problems associated with small sample sizes are low statistical power and the potential for Type II error. When consideration is given to the economic burden of treating chronic pain in adults with SCD, future research studies should include larger sample sizes that represent the breadth and depth of chronic pain in adults with SCD.

Fifth, some of the studies included in this review reported data from subsets of patients from the same sample. While each of these studies reported unique information that adds to the body of research on chronic pain in adults with SCD, the summaries provided in this review may overestimate some of the findings.

Lastly, none of the studies in this literature review defined chronic pain. In addition, it was difficult to distinguish whether the pain reported and measured was acute or chronic pain. While it is known that recurrent vaso-occlusive painful crises may be

considered chronic pain in persons with SCD, it is not clear what determinants of the vaso-occlusive pain episodes constitute to chronic pain in this population. Future studies on chronic pain in adults with SCD should specify criteria for a definition of chronic pain in SCD that is inclusive of the recurrent vaso-occlusive painful crises within the classification of chronic pain described for this population. Furthermore, future studies should include only those participants who meet the inclusion criteria set forth in that definition. It is necessary to have a definition of chronic pain in SCD to help guide treatment and improve pain management for individuals with this disabling condition.

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Table 1

Summary of the Multidimensional Characteristics of Chronic Pain that were Evaluated in Studies of Adults with Sickle Cell Disease

Author, Year	Occurrence	Episodes	Duration	Pattern	Quality	Location	Intensity	Aggravating Factors	Relieving Factors	Functional Status
Anie et al. (2002)		X	X			X	X			X
Ballas et al. (2006)	X	X				X	X			X
Bodhise et al. (2004)	X		X				X		X	X
Booker et al. (2006)		X		X	X	X	X		X	X
Dampier et al. (2002)	X	X	X	X	X	X	X		X	X
Dampier, Ely, et al. (2004)	X	X				X	X			
Dampier, Setty, et al. (2004)		X	X	X		X	X			
Franck et al. (2002)	X	X			X	X	X			
Gil et al. (2004)	X		X				X	X	X	X
Harrison et al. (2005)							X		X	X
Hernigou et al. (2006)	X					X		X		
McClish et al. (2005)		X				X	X	X		X
McClish et al. (2006)	X	X	X			X	X			
Pells et al. (2005)							X	X		X
Platt et al. (1991)	X	X					X			
Sadat-Ali (1993)	X	X		X	X	X	X	X	X	X
Smith et al. (2005)	X	X			X	X	X	X	X	X
Smith et al. (2008)	X	X					X			
Williams & Moskowitz (2007)	X	X								
% of Studies	68%	74%	32%	21%	26%	63%	89%	32%	36%	58%

Table 2

Summary of the Findings from Studies of Chronic Pain in Adults with Sickle Cell Disease

Author/Year **Study Purpose/Design**	**Sample Characteristics** **Variables and Instruments**	**Major Findings**	**Conclusions** **Study Limitations**
Anie, Steptoe, & Bevan (2002) To examine the relationship between pain, coping, and QOL in adult patients with SCD and assess the influence of these factors on health service utilization. Cross sectional study	**N** = 96 **Mean age:** 30.1 ± 8.8 years 33% male, 67% female **Race/Ethnicity:** 52% African, 46% Caribbean, 2% from other areas **SES:** 68% single; 19% married; 13% unknown **Hgb type:** 69% SS, 21% SC, 10% Sβ **Pain status and health service utilization:** Pain Interview **Psychological coping:** Coping Strategies Questionnaire revised for SCD (CSQ-SCD) **QOL:** Medical Outcomes Survey Short Form 36 (SF-36)	**Pain episodes:** 8.11 ± 12.9 episodes in 12 months; **Duration:** 155 ± 156 hours **Pain intensity:** 7.5± 2.7; Bodily pain score on SF-36 = 52.0 ± 29.3 **Relieving factors:** fluids, rest, isolation, praying **Functional status:** Pain had negative effect on physical function and role limitations **Occurrence, pattern, pain descriptors, location, aggravating factors:** NR	**Conclusions:** Patients who reported greater use of active coping strategies experienced more episodes of pain. Patients who used passive coping strategies had higher pain intensity. Patients who reported greater coping strategies had poorer QOL. Pain experience accounted for 12.3% of hospital and general practice services. Psychological coping was unrelated to health service utilization. **Limitations:** No power analysis reported to justify the sample size Sickle cell pain not defined
Ballas et al. (2006) To investigate the effects of hydroxyurea on health related QOL (HQOL) measures in SS patients. RDBPCT study over a two year period	**N** = 299 (277 final analysis) **Mean age:** 33years 49% male, 51% female **Race/Ethnicity:** 95% Black **SES:** Almost all completed HS; 59% unemployed; marital status NR **Hgb type:** 100% SS **Daily bodily pain:** diaries of daily bodily pain **Frequency of pain episodes:** diaries of daily bodily pain **HQOL:** SF-36, Profile of Mood Status (POMS), Ladder of life	**Occurrence:** 44% reported daily chronic pain **Pain episodes:** 56% had ≥ 6 pain crisis annually. All had at least 3 pain crises/year. Hydroxyurea reduced the frequency of pain crises. **Pain intensity: m**ean daily pain scores over four weeks pre-treatment 49% = 1to 3, 35% = 4 to 6, SF-36 bodily pain recall score = 46.5. Significant improvement in 4 week pain recall. **Functional status:** baseline daily pain was a significant independent predictor of several QOL outcomes at all time points **Relieving factors:** See pain intensity **Duration, pattern, pain descriptors, location, aggravating factors:** NR	**Conclusions:** Hydroxyurea improved certain aspects of QOL. Baseline daily pain was a significant predictor on many QOL measures. Although acute pain episodes were reduced, chronic daily pain continued to be high. **Limitations:** Source of chronic pain not reported
Bodhise, Dejoie, Brandon, Simpkins, & Ballas (2004) To evaluate whether deep tissue/deep pressure neuromuscular massage (NMT) reduces pain intensity and opioid consumption and increases relaxation and activities of daily living (ADL) in chronic pain experienced in SCD. Intervention study	**N** = 5 (4 adults & 1 child) with AVN and degenerative disease of the spine **Mean age:** 30 years (adults = 20–44 years, 1 child 12 years of age) 60% male, 40% female **Race/Ethnicity:** 100% African American **SES:** NR **Hgb type:** 40% SS, 40% SC, 20% Sβ **Sickle cell pain:** Numeric Pain Index (NPI) **Typical coping response to stress, pain, changes in mood, expectation of pain management, and economic effect of pain and its treatment:** Tension and Profile of Mood Scale (TPMS) **ADL:** Activities of Daily Living Assessment	**Occurrence**: 100% experienced chronic pain **Pain intensity:** Significant improvement after completion of therapy; pain scores 9.6 ± 0.80 before massage and 2.8 ± 0.75 after massage **Aggravating factors:** N/A **Relieving factors:** NMT **Functional status:** ADL 3.8 ± 0.4 before massage and 1.8 ± 0.75 after massage **Pain episodes:** NR **Duration, pattern, location, pain descriptors:** measured but NR	**Conclusions:** After NMT participants reported relief of pain and tension, a sense of relaxation, and improvement in their ADL that persisted for up to 24–48 hours post NMT. The need for analgesics was reduced for 24 hours in the majority of participants. **Limitations:** Dimensions of chronic pain measured but not reported Limitations not discussed No information provided on recruitment methods
Booker, Blethyn, Wright, & Greenfield (2006) To gain a greater understanding of SCD patients' experience and views of pain management,	**N** = 20 selected, 10 responded. **Mean age:** 32 years 60% male, 40% female **Race/Ethnicity:** Afro-Caribbean, African, and Portuguese	**Pain episodes:** Mild crises managed at home, Medical help needed for severe crises **Pattern:** unexpected and rapid **Pain descriptors:** thousands or millions of needles pinching and	**Conclusions:** Patients with sickle cell pain do not feel that their pain is adequately managed by healthcare professionals owing in part to a lack of understanding by healthcare

Author/Year Study Purpose/Design	Sample Characteristics Variables and Instruments	Major Findings	Conclusions Study Limitations
access to treatment, and relationships with healthcare providers. Cross sectional study - Focus groups obtained through purposive sampling.	**SES**: 50% unemployed, 20% students, 10% employed P/T, 10% volunteer, 10% disabled; 70% single, 30% married **Hgb type:** NR **Pain and pain management strategies:** Focus groups using detailed personal interviews	*jooking*; pain comes in all different shapes and sizes. **Location:** joints and all over the body **Pain intensity:** on a continuum, ranging from mild to severe during a crisis. **Relieving factors:** faith and analgesics **Functional status:** themes: fear, socializing, coping **Occurrence, duration, aggravating factors:** NR	professionals. The impact of social isolation is underestimated in SCD. **Limitations:** Details on chronic pain not reported All participants were users of the resources at the Sickle Cell and Thalassaemia (SCAT) Center where the study took place Relationships of themes to pain dimensions were not specified Effectiveness of the medications was not reported
Dampier, Ely, Brodecki, & O'Neal (2002) To improve the understanding of sickle cell pain (SCP) and its management through the use of home diaries. Longitudinal study up to six months	**N** = 35 **Mean age:** 10.9 years (range – 6 to 19 years) 49% male, 51% female **Race/Ethnicity:** 91.4% African American **SES**: Not reported in this study, but study is part of a larger study in which the majority of the sample was unemployed. **Hgb type:** 72% SS **SCP and other pain:** Pain diaries included 0–10 VAS **Pain descriptors:** APPT **Pain interventions for sickle cell pain:** Pain diaries	**Occurrence:** 98% SCP alone; 97% other pain **Pain episodes:** see duration **Duration:** mean 3.6 days SCP; 3.5days SCP + other pain; 1.6 days other pain alone; range 1–78 days **Pattern:** no difference in pain at night and day **Pain descriptors:** 'steady' common for SCP/SCP + other pain; 'comes and goes' common for other pain **Location:** common sites = legs, right hip, lower back **Pain intensity:** Weighted mean = 5 SCP alone; mean = 7 SCP + other pain **Relieving factors:** analgesics and non-pharmacological methods **Functional status:** pain decreased usual daily activity **Aggravating factors:** NR	**Conclusions:** The use of a home diary was useful in understanding the characteristics of SCP and its management and may be useful as a primary outcome measure for therapeutic trials in SCD. **Limitations:** Definition for SCP narrow; only mentions the acute VOEs, but not chronic SCP Other pain not distinguished as acute or chronic
Dampier, Ely, Eggleston, Brodecki, & O'Neal (2004) To determine the pain management strategies used by children and adolescents, with SCD who manage their pain at home. Longitudinal study	**N** = 39 **Mean age:** 10.9 years (range 6 to 21 years) 49% male, 51% female **Race/Ethnicity:** 92% African American **SES:** NR **Hgb type**: 68% SS **Pain:** Pain diary	**Occurrence:** SCP reported on 14% of days and 13% of nights. **Pain episodes:** mean =11.9 ± 19.6 **Pain intensity:** 1–10 **Relieving factors:** sleeping, hot bath/heating pad, massage, and relaxing/meditation/self hypnosis. Cognitive behavioral and physical activities were used on 84.6% of days with SCP. Analgesic use with cognitive behavioral activities used on 77% of days. Analgesic used alone one 10.9% of days. Cognitive behavioral activities used alone on 7.5% of days. Combination of activities increased with increasing pain intensity **Duration, pattern, pain descriptors, location, aggravating factors, functional status:** NR	**Conclusions:** Cognitive behavioral and physical activities are used frequently for pain in SCD. Combination of activities increased with increasing pain intensity. **Limitations:** Effectiveness of cognitive behavioral and physical activities on pain not measured SCP used interchangeably with sickle cell pain episodes
Dampier, Setty, et al. (2004) To describe the characteristics of home managed painful episodes and to understand the vascular occlusion in SCD. Longitudinal study for up to 6 months	**N** = 30 **Mean age:** 10.6 years (range 6 to 21 years) 57% male, 43% female **Race/Ethnicity:** NR, but included Spanish speaking patients **SES:** NR **Hgb type:** 80% SS, 20% SC **Pain:** Pain diaries included 0–10 (VAS) validity reported **Hematologic and biologic variables:** Laboratory testing	**Pain episodes:** 8 episodes required hospital admission; 40% had at least 1 pain episode/month, 12% had > 2 episodes/month; total of 175 pain episodes **Duration:** 5% of home managed episodes lasted over 2 weeks **Pattern:** unexpected/rapid **Location:** females had greater number of painful sites **Pain intensity:** mild to moderate on most pain days. Severe pain ≥ 7 on 12% of pain days. Younger children reported less intense pain than adults.	**Conclusions:** A direct relationship exists between vaso-occlusive pain and biomarkers. Vaso-occlusive pain can be experienced long after the initial tissue injury has ended. **Limitations:** Chronic and acute sickle cell pain not differentiated Specific pain locations not reported Small sample size limits generalizability

Author/Year Study Purpose/Design	Sample Characteristics Variables and Instruments	Major Findings	Conclusions Study Limitations
		Relieving factors: increased HgF levels associated with longer duration between pain episodes **Occurrence, pain descriptors, aggravating factors, functional status:** NR	
Franck, Treadwell, Jacob, & Vichinsky (2002) To describe the characteristics of pain experienced by children and young adults with sickle cell disease (SCD) and compare the pain experiences in inpatient and outpatient settings. Cross sectional study	**N** = 56 **Mean age:** 15.9 ± 4.32 years 46% male, 54% female **Race/Ethnicity:** African American **SES:** NR **Hgb type:** 84% SS, 9% SC, 7% Sβ **Pain:** APPT Pain measured with VAS 0–100mm	**Occurrence:** 23 clinic visits and 25 day hospital visits r/t pain episodes; 7 clinic visits r/t to pain associated with AVN **Pain episodes:** only reported on number of participants treated for pain episode **Pain descriptors:** used mostly evaluative words; females used more word descriptors **Location:** chest, upper and lower back, and legs; females reported more body areas **Pain intensity:** 5.92 ± 2.62 for clinic patients; 6.99 ± 1.56 for day hospital patients; females reported higher pain intensity **Duration, pattern, aggravating factors, relieving factors, functional status:** NR	**Conclusions:** Older children and young adults reported more body areas with pain ($p < 0.001$) and used more evaluative and temporal words to describe pain ($p < .02$, $p < .04$). Pain intensity, number of body areas with pain, and quality of pain were related to age, sex, and care setting. **Limitations:** Unknown if description of pain specific to pain episodes and/or chronic pain in SCD
Gil, Carson, Porter, Scipio, & Bediako (2004) To analyze daily patterns of pain, positive and negative affect, and stress in adults with SCD over several months. Longitudinal study up to 6 months	**N** = 41 **Mean age:** 36.6 years (range 18 to 71years) 44% male, 56% female **Race/Ethnicity:** African Americans **SES:** 34% less than HS, 56% HS and some college, 10% college degree; 71% disabled, 15% employed, 2% unemployed, 12% students; 56% never married, 22% married, 17% divorced, 5% widowed **Hgb type:** 80% SS, 15% SC, 5% Sβ **SCD pain, other pain and health care use:** Daily diary containing questions modified by the Structured Pain Interview and the Daily Self Monitoring Record; 100 mm VAS scale **Stress:** Daily Diary as above **Mood:** The Daily Mood Scale	**Occurrence:** SCD pain on 33% of diary days. Pain on 168 of 174 days **Duration:** Mean pain duration = 10.1 hours **Pain intensity:** mean = 53.5 on pain days **Aggravating factors:** stress, NA, physical exertion, and exposure to extreme temperatures **Relieving factors:** PA and fluid intake **Functional status:** ratings of SCD pain were significantly and positively associated with same day work absences **Pain episodes, pattern, pain descriptors, location:** not measured	**Conclusions:** Increased daily stress and NA were significantly associated with more SCD pain. PA and higher fluid intake were significantly associated with increased SCD pain **Limitations:** Small sample size Possible bidirectional effects of variables SCD pain not differentiated as chronic SCP or SCD pain crisis Mood was a confounding variable in work absence
Harrison et al. (2005) To examine the association among church attendance, prayer/Bible study, and intrinsic religiosity on measures of pain in adults with SCD. Cross sectional study	**N** = 50 **Mean age:** 36.7 years (range 18 to 70years) 44% male, 56% female **Race/Ethnicity:** 100% African American **SES:** 38% employed, 60% unemployed; 28% less than HS, 32% HS/GED, 20% some college, 2% Graduate school; 26% married, 50% single: 16% divorced, 4% living with a significant other, 2% separated **Hgb type:** 68% SS/Sβ°, 20% SC, 12% other **Pain measures:** McGill Pain Questionnaire Short Form (SF-MPQ), VAS (0–100mm) **Religiosity:** Duke Religious Index **Psychological Distress:** Symptom Checklist-90	**Pain intensity:** lower pain intensity on the VAS ($p<.0004$) and present pain ($p < .0175$) with church attendance **Relieving factors:** church attendance, prayer, Bible study **Functional status:** increased pain associated with higher scores on the Disease Severity Scale **Occurrence, pain episodes, duration, pattern, pain descriptors, location, aggravating factors:** NR	**Conclusions:** Participants who attended church reported lower pain intensity. Multiple regression analysis showed that church attendance was a significant predictor of the sensory, affective, and present experience of pain. **Limitations:** Participants unable to attend church related pain and/or physical disability not examined Small sample size Relationship between religiosity and pain unknown due to cross sectional design

Author/Year Study Purpose/Design	Sample Characteristics Variables and Instruments	Major Findings	Conclusions Study Limitations
	Social desirability: Marlow Crowne Social Desirability Scale **Disease severity:** Combined measure using SCD and self-reported number of pain medications during pain episodes		
Hernigou, Habibi, Bachir, & Galacteros (2006) To define the natural history of asymptomatic osteonecrosis of the femoral head in adults patients with SCD. Longitudinal study, 14 year follow-up	**N** = 121 **Mean age:** 26 years (range 18 to 31 years) 58% male, 42% female **Race/Ethnicity:** NR **SES:** NR **Hgb type:** 40% SS, 48% SC, 12% Sβ **Extent of asymptomatic osteonecrosis:** Steinberg classification system for grading osteonecrosis Harris Hip Score **Clinical progression of osteonecrosis:** Occurrence of pain	**Occurrence:** 91% of participants had pain, 75% had intractable pain requiring surgery. **Location:** hip**s** **Aggravating factors:** progression of symptomatic osteonecrosis **Relieving factors:** hip replacement **Pain episodes, duration, pattern, pain, descriptors, pain intensity, functional status:** NR	**Conclusions:** The occurrence of pain was a significant predictor of collapse in the asymptomatic hip. Pain always preceded collapse of the hips. Time from pain symptom to collapse was 35 months. **Limitations:** Pain intensity not measured
McClish et al. (2005) To assess the health related quality of life (HRQOL) in adults with SCD and compare HRQOL in SCD to other chronic pain conditions. Longitudinal cohort study for up to 6 months	**N** = 308 **Mean age:** 33 years (range 16 to 64 years) 40% male, 60% female **Race/Ethnicity:** NR **SES:** 13% less than high school, 38% HS graduate, 36% some college, 13% college graduate; 22% married, 64% never married, 14% divorced, separated, widowed **Hgb type:** 67% SS, 24 % SC, 3% Sβ°, 3% $Sβ^+$, 3% unknown **HRQOL:** SF-36 **Sickle cell genotype:** medical records **Mean daily pain, percentage of self-reported crisis days, percentage of days with health service utilization:** pain diary	**Pain episodes:** percentage of days with crisis was an independent predictor of bodily pain (p=.01) **Location:** on average 47% of patients reported bodily pain; women reported worse bodily pain **Pain intensity:** Mean daily pain was highly predictive of all subscales on SF-36 except mental health. Increased SCD pain associated with decreased QOL. SF-36 bodily pain score = 47.4. **Aggravating factors:** % of days with crisis **Functional status:** pain had a significant negative impact on physical and social functioning **Occurrence, duration, pattern, pain, descriptors & relieving factors:** NR	**Conclusions:** Participants scored lower than the national norm on all subscales of the SF-36 except mental health. HRQOL decreased significantly as pain increased. **Limitations:** Data on type of mean daily pain associated with SCD not provided Details on pain crisis not provided
McClish et al. (2006) To compare adult men and women with SCD in terms of reported pain, crises, healthcare utilization, and opioid usage. Longitudinal cohort study of up to 6 months duration	**N** = 308 enrolled; 226 completed study **Mean age:** 34 years (range 23 to 56 years) 38% male, 62% female **Race/Ethnicity:** NR **SES:** 12% less than HS, 38% HS graduate, 49% some college **Hgb type:** 69% SS, 24% SC, 2% Sβ°, 3% $Sβ^+$ **Pain measures:** Daily diary including numerical rating scale (NRS) of 0–9 for variables measured **HQOL:** SF-36 **Depression:** PHQ	**Occurrence: m**en = 58.6% pain days; women = 56.5% pain days **Pain episodes:** men with SS/Sβ° genotype experienced more pain crises than women with SS/Sβ°; women with SC/$Sβ^+$ experienced more pain crises than men with SC/$Sβ^+$ **Duration:** consecutive pain crisis days in 6 month period = 7.7 for men and 9.6 for women **Location:** bodily pain **Pain intensity:** during crisis mean pain intensity was 5.5 ± 1.9 for men; 5.6 ± 1.8 for women; mean non crisis pain intensity was 2.5 ± 2.4 for men and 2.2 ± 2.0 for women **Pattern, pain descriptors, aggravating factors, relieving factors, functional status:** NR	**Conclusions:** Women reported worse bodily pain than men. Men and women differed in the frequency of pain crises depending on SCD genotype. **Limitations:** SF-36 not specific to SCP Pain used interchangeably with SCP and pain crisis Unclear if participants experienced chronic pain in addition to frequently occurring acute pain Details regarding pain descriptors used by men and women with SCD not reported
Pells et al. (2005) To explore the relationship between pain severity and BMI in adult patients with SCD. Cross-sectional survey design and medical record review	**N** = 62 **Mean Age:** 37 years for adult patients 53% male, 47% female **Race/Ethnicity:** NR **SES:** NR **Hgb type:** NR **Pain:** LEMPFSCD **Diet/Nutritional Intake:** LEMPFSCD	**Pain intensity:** moderate pain levels of 5.6 resulted in altered eating patterns **Aggravating factors:** perceived current weight **Relieving factors:** not measured **Functional status:** 87% of patients reported that they ate less during episodes of chronic pain	**Conclusions:** Weight had a greater impact on functional ability associated with pain than pain severity. **Limitations:** Retrospective recall of information Unclear if SCD pain versus general pain measured

Author/Year Study Purpose/Design	Sample Characteristics Variables and Instruments	Major Findings	Conclusions Study Limitations
	Psychological distress: LEMPFSCD	**Occurrence, pain episodes, duration, pattern, pain descriptors, location:** not measured	Pain episode not defined although appeared to refer to chronic pain episode
Platt et. al (1991) To study the natural history of sickle cell disease and to understand the characteristics of SCP in individuals with SCD. Longitudinal study	**N** = 3578 **Mean age:** 35% greater than 20 years (range newborn to 66 years) % of males and females: NR **Race/Ethnicity:** Black **SES:** Median income $8900 20% of adults 25 to 59 years were unemployed or disabled; 58% were employed Marital status only provided for 35 to 44 year olds **Hgb type:** 67% SS, 23% SC, 5% $S\beta^+$ 5% $S\beta^\circ$ **Pain rates:** medical records, not clear how pain was measured **Pain episodes:** medical records, not clear how episodes were rated **Health service utilization:** medical records, HbF levels	**Occurrence:** Pain rate of episodes higher for 25–34 year olds **Pain episodes:** 32.9% had 3 to 10 episodes per year **Pain intensity:** patients over 20 years of age with higher pain intensity had more pain episodes and tended to die earlier than those with low rates **Duration, pattern, pain descriptors, location, aggravating factors, relieving factors, functional status:** NR	**Conclusions:** SCP is associated with high mortality in adults over 20 years of age with more than 3 episodes per year. **Limitations:** Participants with hemoglobin of greater than 7 were excluded from the study, even if they could have had sickle cell pain Not clear how pain was measured
Sadat-Ali (1993) To classify the stages of avascular necrosis of the femoral head (ANFH) in SCD. Longitudinal study	**N** = 43 **Mean Age:** 15.5 years (7 to 44 years) 47% male, 53% female **Race/Ethnicity:** 100% Saudi Arabian **SES:** NR **Hgb type:** 100% SC **ANFH:** Classification system using integrated factors of patient's history, clinical findings, and radiologic picture	**Occurrence:** 100% had AFNH and experienced some form of pain. **Pain episodes:** chronic pain **Pattern:** pain severity worse with Grade progression **Pain descriptors:** Grade I vague pain; Grade II constant pain; Grade III moderate to severe; Grade IV severe to unbearable **Location:** hips, groin, back **Pain intensity:** vague to unbearable **Aggravating factors:** flexion, abduction, adduction **Relieving factors:** Grade II required analgesics; Grade IV required surgical intervention to relieve pain and increase mobility. **Functional status:** physical activity limited and decreased mobility **Duration:** NR	**Conclusions:** Early diagnosis of AFNH is needed to avoid complications associated with the disease. AFNH divided into 4 Grades with the patient experiencing progressively worse pain and functional limitations with each increase in grade. **Limitations:** No measurement tool for pain reported Duration of pain not reported
Smith, Coyne, Smith, Roberts, & Smith (2005) To test the effects of an intrathecal drug delivery systems (IDDS) for refractory chronic bone pain associated with SCD. Cross sectional, case study	**N** = 2 **Mean Age:** Case 1 = 52 years of age; Case 2 = 27 years of age Both female **Race/Ethnicity:** NR **SES:** NR **Hgb type:** 100% SC **Chronic sickle cell anemia bone pain:** VAS	**Occurrence:** Frequent **Pain episodes:** Case 2 averaged 6–7 hospital admissions for pain crisis per year, sometimes as many as every 2–3 weeks. **Pain descriptors:** severe **Location:** chronic bone pain multiple bones; shoulder and hips **Pain intensity:** Case 1=10/10 Case 2=7/10 at rest; 10/10 with ambulation. **Aggravating factors:** ambulation; **Relieving factors:** analgesics for breakthrough pain; Case 1= IDDS of 13.2 mg of morphine per day. Case 2 = 5.8mg of hydromorphone per day **Functional status:** decreased physical activity and mobility **Duration, pattern:** NR	**Conclusions:** An IDDS reduced refractory chronic bone pain and improved normal activity in two adults with SCD. More research is warranted on the use of IDDS for chronic pain in adults with SCD. **Limitations:** Impact of acute sickle cell pain episodes on chronic pain not measured or reported Limited information on quality of pain. No information on duration or pattern of pain
Smith et al. (2008) To examine the prevalence of self-reported pain and the relationship among pain	**N** = 232 **Mean Age:** 16 to 64 years 62% male, 38% female **Race/Ethnicity:** NR	**Occurrence:** 29% had chronic pain (pain nearly every day of study period)	**Conclusions:** Adults with SCD experience pain more frequently than previously reported. Healthcare providers should trust reports of pain in patients with SCD

Author/Year Study Purpose/Design	Sample Characteristics Variables and Instruments	Major Findings	Conclusions Study Limitations
crises and utilization in adults with SCD. Longitudinal prospective cohort study (6 months)	**SES:** 12% less than HS, 38% HS graduate, 35% some college, 15% college graduate; 24% married, 62% never married, 14% divorced, separated, widowed; Majority income less than $10, 000 **Hgb type:** 73% SS/ Sβ°, 27% SC/ $S\beta^+$ **Self reported pain, crisis, and health care utilization:** daily diary	**Pain episodes:** patients did not seek treatment for pain crises on 13% of days **Pain intensity:** Mean pain intensity without crisis = 4; crisis without utilization = 5; health care utilization with or without crisis = 6. Mean pain intensity increased as number of pain days increased **Duration, pattern, pain descriptors, location, aggravating factors, relieving factors, functional status:** not measured	and give attention to outpatient treatment, as well as inpatient treatment. More than half of patients (54%) reported pain on more than half of the days. **Limitations:** Pain variable not defined SCD pain not differentiated from other types of pain
Williams & Moskowitz (2007) To investigate the effects of Trandoloapril on pain in SCD. Longitudinal case study	**N** = 1 **Mean Age:** 48 year old female **Race/Ethnicity:** African American **SES:** NR **Hgb type:** SS **Pain** - No information on pain measurement	**Occurrence:** daily pain episodes for as long as patient could remember **Pain episodes:** 3–4 episodes per year **Pattern:** worse during winter months **Pain descriptors:** severe **Location:** joint pain in the elbows, hips, and knees **Aggravating factors:** frequency and severity of pain episodes worsened during winter months **Relieving factors:** pain episodes treated with fluids, analgesics, and occasional blood transfusions. Joint pain treated with 2–6 hydrocodone and acetominophen tablets per day and hot baths. **Pain intensity, duration, functional status:** NR	**Conclusions:** Trandolapril 1mg per day reduced patient's pain and the need for other analgesics for greater than 12 months. ACE inhibitors may play a role in pain management in adults with SCD. **Limitations:** Limited information on characteristics of acute pain and chronic joint pain Effect of pain on functional status not reported

Abbreviations: ACE - angiotensin 1-converting enzyme, AFNH – avascular necrosis of the femoral head, APPT – Adolescent Pediatric Pain Tool, AVN – avascular necrosis, BMI – Basal Metabolic Index, GED – General Education Development certificate, HbF – fetal hemoglobin, HQ – Patient Health Questionnaire, HS – high school, LEMPSCD - Longitudinal Exploration of Medical and Psychosocial Factors in SCD, NA – negative affect, NR – not reported, PA – positive affect, P/T – part time, QOL – quality of life, RDBPCT – Randomized Double Blind Placebo Controlled Trial, r/t – Related to, Sbeta zero (Sβ°) – sickle beta zero thalassemia, Sbeta plus ($S\beta^+$) – sickle beta plus thalassemia, SC – one sickle hemoglobin gene and one abnormal hemoglobin 'C'gene, SCD – Sickle Cell Disease, SCP – sickle cell pain, SS – two sickle hemoglobin genes (Sickle Cell Anemia), VAS – Visual Analog Scale

Table 3

Various Types of Pain that were Evaluated in Studies on the Prevalence/Incidence of Chronic Pain in Adults with Sickle Cell Disease

Author, Year	Sample Size	Chronic Pain	Recurring Acute Pain Crises	Mixed Pain (% Chronic Pain)
Anie et al. (2002)	96		X	
Ballas et al. (2006)	299			X
Bodhise et al. (2004)	5	X (100%)		
Booker et al. (2006)	10		X	
Dampier et al. (2002)	35			X
Dampier, Ely et al. (2004)	39			X
Dampier, Setty, et al. (2004)	30		X	
Franck et al. (2002)	56	X	X	
Gil et al. (2004)	41			X
Harrison et al. (2005)	50		X	
Hernigou et al. (2006)	121	X (100%)		
McClish et al. (2005)	308			X
McClish et al. (2006)	226			X
Pells et al. (2005)	62	X (100%)		
Platt et al. (1991)	3578		X	
Sadat-Ali (1993)	43	X (100%)		
Smith et al. (2005)	2			X (100%)
Smith et al. (2008)	232			X (29%)
Williams & Moskowitz (2007)	1			X (100%)
Total Number of Studies from 19	5234	5	6	9

Note: Percentages for participants with chronic pain given only for those studies providing details on this information

Table 4

Pain Descriptors Used for Chronic Pain in Adults with Sickle Cell Disease

Descriptor	Booker et al., 2006	Dampier et al., 2002	Franck et al., 2002	Sadat-Ali, 1993	Type of Chronic Pain
Aching			X		Chronic, Recurring Acute, Mixed
Awful		X	X		Chronic, Recurring Acute
Annoying			X		Chronic, Recurring Acute
Bad			X		Chronic, Recurring Acute
Comes all of a sudden	X	X	X		Chronic, Recurring Acute, Mixed
Comes and goes		X	X		Chronic, Recurring Acute, Mixed
Comes in all different shapes and sizes	X				Recurring Acute
Comes on slowly		X			Mixed
Constant			X	X	Chronic, Recurring Acute
Continuous			X		Chronic, Recurring Acute
Crying			X		Chronic, Recurring Acute
Dizzy			X		Chronic, Recurring Acute
Frightening		X			Mixed
Hurting			X		Chronic, Recurring Acute
Jooking!	X				Recurring Acute
Miserable		X	X		Chronic, Recurring Acute, Mixed
Off and on			X		Chronic, Recurring Acute
Pressure			X		Chronic, Recurring Acute
Severe				X	Chronic
Sneaks up			X		Chronic, Recurring Acute
Steady		X	X		Chronic, Recurring Acute, Mixed
Throbbing			X		Chronic, Recurring Acute
Thousands or millions of needles pinching you	X				Recurring Acute
Tingling	X				Recurring Acute
Unbearable		X			Mixed
Uncomfortable		X	X		Chronic, Recurring Acute, Mixed
Unexpected	X				Recurring Acute
Vague				X	Chronic
Total number of descriptors from 28	6	9	18	8	

Table 5

Common Sites of Chronic Pain in Adults with Sickle Cell Disease

Location	Bodhise et al., 2004	Booker et al., 2006	Dampier et al. 2002	Dampier et al., 2004	Franck et al., 2002	Hernigou et al., 2006	Sadat-Ali 1993	Smith et al., 2005	Williams & Moskowitz, 2007
Abdomen					19%				
All over body		10%							
Arm					7%				
Back	60%		X	X	99%		23%		
Chest				X	81%				
Elbow joints									100%
Groin							30%		
Hips	60%		X	X		100%	70%		100%
Legs			X	X	90%				
All joints		10%							
Knee joints									100%
Shoulder	20%								
Multiple bones/ areas	40%	10%	X	X	5%		23%	100%	100%

Total of 13 sites

Note: Weighted means for back pain (60%), hip pain (80%), and multiple bones/areas (14%)

Table 6

Strategies Used to Relieve Chronic Pain in Adults with Sickle Cell Disease

Strategy	Anie et al., 2002	Bodhise et al., 2004	Booker et al., 2006	Dampier et al.,2002 2004a 2004b	Gil et al., 2004	Harrison et al., 2005	Hernigou et al., 2006	McClish et al., 2006	Sadat-Ali, 1993	Smith et al., 2005	Smith et al., 2008	Williams & Moskowitz, 2007
Analgesics	X		X	X (a,b)				X	X	X	X	X
Bible Study						X						
Calming Statements	X											
Church attendance						X						
Cold	X											
Communication				X (a)								
Faith/ Hoping	X		X									
Fluids	X				X							X
Heat	X			X (a)								
Hot bath				X (a)								
Isolation	X											
Increasing activity	X											
Massage		X		X (a)								
Meditation				X (a)								
Positive mood					X							
Praying	X			X (a)		X						
Reading				X (a)								
Relaxation	X			X (a)								
Self-hypnosis				X (a)								
Sleep				X (a)								
Surgery							X		X			
Watch TV				X (a)								
Total number of studies = 22	10	1	2	1 (b) 24 (2002a)	2	3	1	1	2	1	1	2

Chapter 3.

Occurrence and Characteristics of Persistent Pain in Adult Outpatients with Sickle Cell Disease

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Occurrence and Characteristics of Persistent Pain in Adult Outpatients with Sickle Cell Disease

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Key Words: sickle cell disease, persistent pain, pain characteristics, breakthrough pain, pain severity, chronic pain, pain crises, vaso-occlusive episodes

Abstract

Persistent pain from Sickle Cell Disease (SCD) is a multidimensional experience that affects every aspect of an individual's life. However, a review of the literature suggests that significant gaps exist in our knowledge of the occurrence and characteristics of persistent pain in adults with SCD. This descriptive, cross sectional study investigated the occurrence and multidimensional characteristics of persistent pain in 103 adult outpatients with SCD and compared patients with manageable and unmanageable pain on a number of demographic and clinical characteristics and a variety of pain measures (i.e., pain characteristics, pain qualities, pain behaviors, pain interference). Of 94 patients with persistent pain, 70% had manageable pain and 30% had unmanageable pain. Of 85 patients who provided information on breakthrough pain (BTP), 81% experienced BTP. Patients with unmanageable pain reported higher ratings for all of the items on the Pain Quality Assessment Scale (PQAS); experienced more BTP, had a higher frequency of BTP during the day, reported more locations of BTP; were more likely to be taking only a short-acting opioid; reported less relief from pain medications; and were more likely to live alone. These findings suggest that persistent pain in adults with SCD is a significant clinical problem.

Perspective: This article fills some of the gaps in the research on persistent pain in adults with SCD by investigating the occurrence and characteristics of this significant problem. Results of this study provide better understanding of persistent SCD pain and may lead to improved pain management for this vulnerable population.

Introduction

Sickle cell disease (SCD) is a chronic genetic blood disorder plagued by acute and persistent pain. In fact, acute pain is the most common symptom reported by persons with SCD.[48-50] Due to advances in treatment, persons with SCD are living well into adulthood. However, most of the research on SCD pain has focused on acute pain in children.[3,17,28,33,64,66] Despite evidence that acute pain often becomes persistent pain in adults with SCD and that persistent pain is a serious problem,[6,49,50] significant gaps exist in our knowledge of the occurrence and multidimensional characteristics of persistent SCD pain in adults.

Additional data on the occurrence and characteristics of persistent pain in adults with SCD is needed to fully understand the impact of this condition. In a review of the literature on the multiple dimensions of persistent pain in adults with SCD,[66] the occurrence of persistent pain ranged from 29% to 100% with a weighted mean occurrence rate of 65%. However, some studies included children and had small sample sizes, making it difficult to estimate the occurrence of persistent pain in adults with SCD and understand its characteristics.

Due to the multidimensional nature of persistent pain,[15,68] effective treatments can be challenging. As in other persistent pain conditions, persistent SCD pain is often managed with pharmacologic and non-pharmacologic interventions.[11,21,45] Consistent with research in other persistent pain conditions,[12] short- and long-acting opioids or a combination of both formulations are commonly prescribed for adults with moderate to severe persistent SCD pain.[60,61]

Despite the use of prescription analgesics, adults with persistent SCD pain experience inadequate pain relief.[7,60,62] Common reasons for inadequate pain relief in this

population are varied and complex and include undertreated pain, fear of addiction, fear of accurately reporting pain, and inappropriately prescribed analgesics.[7,36,39,76] Most of the studies that reported these findings focused on acute pain in adults in an acute care setting. No studies were identified that investigated the types of prescription analgesics used by adults with persistent SCD pain in an outpatient setting.

Individuals with persistent pain often experience breakthrough pain (BTP). Multiple definitions exist for BTP, such as a transitory exacerbation of pain that occurs in addition to persistent stable pain; a transitory increase in pain levels to greater than moderate intensity superimposed on a baseline pain of moderate intensity or less in patients receiving long-term opioid therapy; or the act of breaking through pain relief.[4,40,54,77] Despite the lack of a clear definition, BTP is well characterized in patients with cancer pain,[24,51,53] but less is known about BTP associated with non-cancer pain.[25,51,54,55] No studies were identified that reported the characteristics and occurrence of BTP in adults with persistent SCD pain.

Recently, work by Zelman and colleagues introduced the concept of "manageable pain" (i.e., average daily pain ≤ 5) in patients with a number of chronic pain conditions.[74,75] However, no studies have evaluated for differences in pain characteristics and analgesic prescriptions in patients with SCD who have manageable versus unmanageable persistent pain. Given the paucity of research on persistent SCD pain, the purposes of this study were to describe the occurrence and multidimensional characteristics of persistent pain in adults with SCD and to evaluate for differences in pain characteristics between those with manageable and unmanageable persistent SCD pain.

Materials and Methods

Sample and Settings

Patients were eligible to participate if they were at least 18 years of age; had SCD and persistent pain of at least 3 months duration; managed their pain at home; had not been hospitalized for more than 14 days in the past month; had SCD, but did not have persistent pain; and were able to read and write in English. A total of 146 patients enrolled in the study. Of those, 71% (n=103) completed a series of self-report questionnaires. Patients were recruited during clinic visits at the Adult Sickle Cell Clinic of the University of California San Francisco/San Francisco General Hospital (UCSF/SFGH) and Children's Hospital and Research Center, Oakland (CHRCO); through Facebook; at bay area churches, colleges, local and national SCD organizations; and through snowball sampling.

Instruments

Demographic Characteristics

Patients provided information on gender, age, race/ethnicity, education, marital status, living arrangements, employment status, and annual income. Patients self-reported their SCD type.

Clinical Characteristics

Self-Administered Comorbidity Questionnaire (SCQ) - The presence of comorbid conditions was evaluated using the SCQ.[58] The SCQ contained 13 defined and three optional medical conditions. The maximum total score was 39 (1 point each for the presence of the condition, 1 point if the patient received treatment for the condition, and 1 point if the condition caused a limitation in functioning) for the 13 defined medical

conditions and 48 when the three optional conditions were included. Higher scores indicate more medical conditions and a greater impairment. The SCQ has well-established validity and reliability in other persistent pain conditions.[14,42]

Karnofsky Performance Status Scale (KPS) - The KPS scale measures a patient's ability to accomplish normal activities of daily living and their need for assistance based on the definitions provided on a 0 to 100 (%) rating scale, in increments of 10%.[34] The KPS scale consisted of eight items that patients used to rank their functional status. The items ranged from 30 (i.e., disability requiring hospitalization) to 100 (i.e., adequate health status with no complaints and no evidence of disease). The KPS has well-established validity and reliability and has been used extensively in persistent pain populations.[14,15,46]

Characteristics of Persistent Pain

Patients answered the following pain question to determine the occurrence of persistent pain: "Do you have pain and/or are you taking pain medicine or other treatments for your pain? Patients who answered "Yes" were prompted to answer additional questions about their persistent pain.

Cause(s) of Pain

Patients were asked to indicate the cause(s) of their persistent pain among three prespecified choices (i.e., their SCD; the effects of treatment (e.g., medication, surgery) for their SCD; a medical condition unrelated to their SCD).

Brief Pain Inventory (BPI) and Length of Time in Persistent Pain

Using items from the BPI,[30] patients were asked to rate the intensity of their pain (i.e., pain right now, average pain, worst pain, least pain) using a 0 (none) to 10 (excruciating) numeric rating scale (NRS). A NRS is a valid and reliable measure of pain

intensity. Information on frequency of pain was obtained by asking patients to rate how many days (0 -7) out of a typical week they currently had pain that interfered with their mood and/or activities. Duration of patients' pain was evaluated by asking how many hours of the day (0 -24) their pain lasted. In addition, patients were asked how long they had been in pain. Patients were asked to list current prescription analgesics, the amount of pain relief from their pain medicine in the last week, and satisfaction with pain treatment overall. The BPI is a valid and reliable self-report instrument designed to measure the multiple dimensions of persistent pain,[13,65] and has been used to study pain in adults with SCD.[7]

Pain Quality Assessment Scale (PQAS) - Patients rated the severity of 20 pain qualities over the past week using the PQAS, (i.e., 16 pain qualities (e.g, shooting, cramping), two global domains (i.e., pain intensity, unpleasantness), and two spatial domains (deep and surface pain)).[32] The PQAS uses a 0 (no pain or sensation not experienced) to 10 (the most pain (descriptor) sensation imaginable) NRS. Three subscales were created from 15 items on the PQAS that assessed Paroxysmal (i.e., shooting, sharp, electric, hot, and radiating items), Surface (i.e., itchy, cold, numb, sensitive, and tingling items) and Deep (i.e., aching, heavy, dull, cramping, and throbbing items) pain.[32] The PQAS is a valid and reliable measure to assess pain qualities in patients with persistent pain.[35,43]

Pain Crises Severity and Last Sickle Cell Pain Crisis - The Sickle Cell Disease Pain Crisis instrument was used to evaluate the characteristics of a patient's pain crisis.[19] Patients were asked the question 'When was your last sickle cell pain attack (crisis)? In addition, patients were asked to rate the severity of pain during their last 'pain attack' and the duration of their last pain crisis. The Sickle Cell Disease Pain Crisis instrument is a

subscale of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me), which was validated for use in adults with SCD.[19]

Characteristics of BTP - Patients who reported that they experienced BTP, were asked to describe its intensity, location, frequency, duration, and predictability.

Patient Reported Outcome Measurement Information System (PROMIS) – Pain Behavior-Short Form (SF) - Patients rated how frequently they engaged in four categories of external manifestations of pain behaviors (i.e., distorted ambulation, affective distress, facial/audible expressions, help seeking behaviors) in the past 7 days using the PROMIS Pain Behavior-SF.[56] The reported actions or reactions can be verbal or non-verbal and involuntary or deliberate. Each of the seven items on the Pain Behavior-SF is scored on a 6-point Likert scale, that ranges from 1 (had no pain) to 6 (always). Higher scores indicate worse functioning or more symptoms. The PROMIS Behavior-SF is a valid and reliable instrument.[56]

PROMIS – Pain Interference-Short Form (SF) - Patients self-reported the degree to which pain limited or interfered with their physical, mental, and social activities in the past seven days using the Pain Interference-SF. Each of the six Pain Interference-SF items has five response options that range from 1 (Not at all) to 5 (Very much). Higher scores indicate a greater degree of pain interference. The PROMIS Pain Interference-SF demonstrated good validity and reliability.[2]

Analgesic Medications and Pain Treatments

Patients listed any analgesic medications they were taking. Patients were asked to rate the percent of relief they received from their analgesics using a 0% (no relief) to 100% (complete relief) NRS; satisfaction with pain treatment overall using a 0

(extremely dissatisfied) to 10 (extremely satisfied) NRS; and how long it took before their pain returned. Analgesic medications were categorized into opioid, non-opioid, and co-analgesics.

Opioid Analgesics

Opioid analgesics were classified as short-acting (e.g., oxycodone, acetaminophen with codeine) and long-acting (e.g., methadone, controlled release morphine). The patient's opioid prescription was categorized into one of four categories: no opioids, only short-acting opioids, only long-acting opioids, or both short- and long-acting opioids.

Non-opioid Analgesics and Co-Analgesics

Non-opioid analgesics were classified as non-steroidal anti-inflammatory drugs (NSAIDS). Co-analgesics were classified as anticonvulsants, tricyclic antidepressants (TCAs), non-TCAs, benzodiazepines, muscle relaxants, and marijuana.

Procedures

The study was approved by the Committee on Human Research at UCSF and the Institutional Review Board at CHRCO. Informed consent was obtained from each patient. A letter of referral for eligible patients along with an Information Study Sheet was provided to the physicians and nurse practitioners at the study sites. Staff approached patients during clinic visits. Interested patients were referred to the researcher (LT), either in person at the clinic or by phone. In addition, patients contacted the researcher (LT) after seeing a flyer about the study.

Potential patients were screened and the study purposes and procedures were described in person or by phone. After obtaining informed consent, a total of 146 patients were enrolled in the study. Five patients were enrolled through the clinics at UCSF/SFGH

and 68 patients through the clinic at CHRCO. Of these 73 patients, 74% (n=54) completed the study questionnaires. Thirty-eight patients were enrolled through the Sickle Cell Disease Foundation of California and 84% (n=32) completed the study. One patient was enrolled from a bay area church, six patients from conferences, four patients through Facebook, and 24 patients through snowball sampling. Of these 33 patients, 52% (n=17) completed the study questionnaires.

Enrolled patients were asked to complete the study questionnaires either in paper format (n=67) or online (n=36). Patients were given approximately one week to complete the questionnaire booklet. Patients were contacted after one week by phone or e-mail if they had not completed and returned the booklet via a prepaid envelope or made arrangements to have the booklet picked up by the researcher (LT). Patients received a $20 gift card, journal, and writing pen to compensate them for completing the study questionnaires.

Data Analysis

All data analyses were done using IBM Statistical Package for the Social Sciences, Version 20.0. (IBM Corporation, Armonk, NY). Descriptive statistics were used to describe the patients' demographic and clinical characteristics. Based on the work of Zelman and colleagues,[74,75] ratings of average pain were used to categorize patients with manageable (≤5 = mild pain) or unmanageable (>5 = moderate to severe) pain.

Differences between the two pain groups in demographic and clinical characteristics, pain characteristics, pain crisis characteristics, BTP characteristics, pain behaviors, pain interference, and use of prescribed analgesics were evaluated using independent sample t-tests and Chi-square analyses. Patients' raw scores for the Pain

Behavior-SF and Pain Interference-SF were converted to a T-score. The T score converts the raw score into a standardized score with a mean of 50 and standard deviation (SD) of 10. For all analyses, a p-value of <.05 was considered statistically significant.

Results

Occurrence of Persistent Pain

Of the 103 patients who completed the study, 93% (n=96) reported persistent pain or the use of analgesics. Of the 96 patients who reported pain, 98% (n=94) rated their average daily pain. All remaining analyses were done with these 94 patients. Of these 94 patients, 66 (70%) had manageable pain and 28 (30%) had unmanageable pain. Fifty seven percent (n =52) of the patients reported being in pain for more than one year. Of the 52 patients who reported being in pain for more than one year, the average length of time they were in pain was 21.4 (SD=15.4) years. Approximately 27% of these 52 patients had been in pain since infancy. The two pain groups did not differ in the length of time patients were in pain.

Differences in Demographic and Clinical Characteristics Between the Pain Severity Groups

The majority of the patients were female (67%), Black/African American (97%), had an average age of 36.7 (SD=13.1) years and had 13.9 (SD=2.5) years of education (Table 1). Approximately 27% of patients lived alone, 57% were never married, 70% were unemployed, and 62% had an annual income of less than $20,000 per year. Except for living arrangements, no differences in demographic characteristics were found between the two pain groups. A higher percentage of patients with unmanageable pain lived alone (p=.04).

Most of the patients (73%) reported having hemoglobin type SS (HbSS). The mean SCQ score was 6.5 (± 3.8). SCD type and SCQ score did not differ between groups. The mean KPS score was 76.0 (SD=15.3). Patients in the unmanageable pain group reported a lower KPS score (70.7 ± 14.7) than those in the manageable pain group (78.2 ± 15.1, p=.03).

Differences in Cause(s) of Persistent Pain Between the Pain Severity Groups

A higher percentage of patients in the unmanageable pain group (54%) attributed their pain to the effects of treatment for SCD (p=.04). Of the total sample, most patients (99%) reported SCD as the cause of persistent pain and 23% attributed their pain to a medical condition unrelated to their SCD. No differences were found between the two pain groups for these two findings.

Differences in Pain Characteristics Between the Pain Severity Groups

Most of the pain characteristics differed between the two pain groups (Table 2). Compared to the manageable pain group, patients in the unmanageable pain group reported higher pain intensity and interference scores, as well as, a higher number of days per week in pain, less satisfaction with pain treatment, and lower levels of pain relief. For the total sample, the mean T scores for pain behaviors and pain interference were 55.7 (SD=5) and 64.3 (SD=6.2), respectively. No differences in either score were found between the two pain groups.

Differences in Pain Qualities Between the Pain Severity Groups

All of the pain quality ratings, as well as the subscale scores, on the PQAS differed between the pain groups (Table 2). Patients in the unmanageable pain group reported higher ratings for all of the pain qualities. The pain quality with the highest

rating was ‘deep’ (6.5, SD=2.8, p<.0001) followed by ‘unpleasant’ (6.3, SD=2.8, p<.0001). The pain qualities with ratings 5.0 and above were sharp, aching, intense, throbbing, unpleasant, and deep.

Differences in Pain Crises Between the Pain Severity Groups

Pain crisis characteristics (i.e., frequency of pain crises in the past 12 months, occurrence of the last pain crisis, duration of last pain crisis, severity of pain) did not differ between the two groups (Table 3).

Differences in BTP Characteristics Between the Pain Severity Groups

Of the 85 patients who provided information on BTP, 81% (n=69) reported that they experience BTP (Table 4). A higher percentage of patients in the unmanageable pain group reported experiencing BTP (p=.02). These patients reported experiencing BTP an average of 3.1 (SD=2.2) times per day compared to 2.0 times per day for patients in the manageable pain group (p=.02). Approximately 45% of the patients reported experiencing BTP in the same location as their usual pain, 26% in a different location than their usual pain, and 12% reported experiencing BTP in both locations. Compared to the manageable pain group, a higher percentage of patients in the unmanageable pain group reported experiencing BTP in both similar and different locations from their usual pain (p=.02). Approximately 80% of patients reported that their BTP was unpredictable and 81% reported that it occurred spontaneously. The average duration was 38 minutes. No differences were found between the two pain groups in any of these characteristics.

Differences in the Types of Analgesic Prescriptions Between the Pain Severity Groups

Most patients (87%) reported taking prescription analgesics (Table 5). Opioids were the most commonly prescribed analgesic. The majority of the patients who were

taking opioids (67%) were taking only a short-acting opioid. Approximately 3% were taking only a long-acting opioid and 22% were taking both a short- and a long-acting opioid. The types of opioid analgesic prescriptions did not differ between the two pain groups. Approximately 32% of patients reported taking a prescription NSAID. Only 1% reported taking an anticonvulsant, muscle relaxant, or marijuana for their pain.

Discussion

This study is the first to evaluate the occurrence of persistent pain in adults with SCD and provide a detailed characterization of their pain. While the original intent was to evaluate for differences in demographic and clinical characteristics between patients with and without persistent pain, 93% of the patients reported persistent pain or the use of analgesic medications. Therefore, these patients were divided into manageable (70%) and unmanageable (30%) groups for subsequent comparisons using Zelman and colleagues categorization.[74,75]

Consistent with reports of persistent pain in adults with HIV[45] and patients with terminal cancer,[70] 93% of the patients in this study reported persistent pain for an average of 3 months or longer. This occurrence rate is higher than the 29%[5] and 44%[63] reported in previous studies of adults with SCD. These differences in occurrence rates may be related to the recruitment methods used in each study. Whereas, the present study asked patients during screening if they had chronic pain (i.e., pain ≥ 3 months), no specific screening procedures were identified in the previous two studies that evaluated for the presence of persistent pain.

The manageable and unmanageable pain groups experienced persistent pain for a similar length of time. In fact, consistent with two previous studies,[60,61] 27% of the

sample reported that they were in pain since infancy. These findings suggest that a significant percentage of adults with SCD experience persistent pain for a significant proportion of their childhood and adult life. This characteristic distinguishes pain from SCD from other causes of persistent pain.[16,50,60,61]

Consistent with two previous reports,[23,50] 99% of the patients attributed the cause of their pain to SCD. However, in this study, particularly in the unmanageable pain group, 33% reported that pain was attributed to their SCD treatments. Unfortunately, detailed information on which treatments contributed to persistent pain was not collected (e.g., pain from SCD related comorbidities) and warrants investigation in future studies.

Compared to the most recent study of persistent pain from recurrent pain crises in adults with SCD,[73] patients in this study reported higher pain intensity scores, less satisfaction with treatment, and less pain relief. As expected, the unmanageable pain group reported significantly higher pain intensity scores than the manageable pain group. Of note, the average pain intensity scores for the persistent pain experienced by the unmanageable group, were similar to pain scores reported by patients during vaso-occlusive episodes (VOEs).[38,63] This finding suggests that a third of adult patients with persistent pain from SCD experience pain of comparable intensity to a VOE on a daily basis. However, in contrast to findings from two studies,[39,63] no between group differences were found in any of the pain crisis characteristics that were evaluated (Table 3). One consideration is that the pain associated with VOEs can range from mild to severe pain in its intensity[10,27] and vary in duration within individuals. Longitudinal studies are needed to evaluate the variable nature of persistent pain, as well as, pain associated with VOEs in adults with SCD.

This study is the first to use the PQAS to evaluate pain qualities in adults with persistent SCD pain. Consistent with a previous study of adults with persistent pain from HIV disease,[45] the pain qualities with intensity ratings of ≥5 were deep, unpleasant, throbbing, intense, aching, and sharp. While all of the pain quality scores were significantly higher in the unmanageable group, the same six qualities had the highest scores in both pain groups. Overall, patients in our study reported higher scores for paroxysmal and deep pain than surface pain, which is similar to previous studies of patients with persistent pain from other conditions (i.e., HIV disease,[45] low back pain,[71] osteoarthritis,[71]diabetic neuropathy,[31] postherpetic neuralgia[22]). These findings suggest that adults with persistent SCD pain experience both neuropathic[22,31,45] and non-neuropathic pain.[71] An evaluation of the pain qualities associated with persistent pain in adults with SCD may assist clinicians in prescribing analgesic medications for specific types of pain in these patients.

This study is the first to characterize BTP in adults with SCD. The two pain groups were similar for the majority of BTP characteristics. Compared to BTP occurrence rates of 50% to 90% in oncology patients[9,41,42,51] and 50% to 75% in patients with non-cancer pain,[8,51,52] 81% of the patients with persistent SCD pain reported BTP. Of note, a significantly higher percentage of patients in the unmanageable group reported BTP. All of the characteristics of BTP in these patients with persistent pain from SCD are similar to findings of BTP in patients with cancer[9,24,42] and non-cancer pain.[8,9,51]

An unexpected finding in this study was that no differences were found between the two pain groups in the various types of analgesic prescriptions, especially since the pain scores were higher in the unmanageable pain group. An evaluation of the worst pain

scores for the total sample in this study (i.e., 8.2) is consistent with previous studies that concluded that persistent pain in adults with SCD is undertreated.[18,37,47] In terms of the types of opioid analgesic prescriptions, no differences were found between the two pain groups. In both pain groups, 3% of the patients were prescribed only a long-acting opioid and 22% of the patients were prescribed both a short- and a long-acting opioid. These percentages are higher than those reported in a study of persistent pain from HIV disease (i.e., 35% had a short-acting opioid, 8% had both a short- and long-acting opioid).[45] On the other hand they were lower than percentages reported for patients with cancer pain (i.e., 36% had only a short-acting opioid, 37% had both a short- and long-acting opioid).[44] This finding suggests that use of long-acting opioids for persistent pain is not common in two vulnerable patient groups (i.e., SCD and HIV disease). Future studies need to explore the reasons for the variations in opioid prescribing practices across a variety of persistent pain problems.

A surprising finding is that almost none of the patients in either pain group were prescribed any co-analgesics. The reason why antidepressants and anticonvulsants that are effective in other persistent pain conditions,[45,72] are not prescribed in patients with SCD warrants investigation in future studies. In contrast with another study that found that 29% of patients used marijuana for SCD pain,[26] only one patient in the study reported that s/he had a prescription for marijuana. As in the previous study,[26] patients in our study did not report on whether or not they had a prescription for the marijuana.

With the exception of functional status and living arrangements, the pain groups were similar in demographic or clinical characteristics and consistent with those in previous studies of adults with SCD.[1,29,39,57,63] Patients with unmanageable pain reported

significantly lower functional status scores. This difference represents not only a statistically significant, but clinically meaningful difference (d=0.5).[59] An interesting observation is that the patients with SCD who were only 36 years of age had KPS scores similar to those of oncology patients who were 60 years of age and older.[69] A higher percentage of patients in the unmanageable pain group lived alone. This finding is significant because in two previous studies of adults with persistent pain,[20,67] a higher level of social support was associated with lower pain intensity scores. Future studies need to explore the association between social support and persistent pain in adults with SCD.

This study has a number of limitations. The pain characteristics reported in this study are based on self-report and did not incorporate a physical examination to verify the cause of the pain and validate functional status. Data were not obtained on the doses of analgesic medications that were prescribed for these patients. Because this sample was a convenience sample, the pain occurrence rates may be an over-estimation. In addition, comparisons between patients with and without persistent pain from SCD could not be done because only seven patients without pain were recruited into this study. Longitudinal studies, with larger sample sizes, are needed to assess the unique characteristics of persistent pain in this population and how they change over time.

Despite these limitations, our findings suggest that moderate to severe persistent pain compounded by recurrent VOEs and BTP is a daily occurrence in the lives of a large percentage of adults with SCD. Moreover, findings from this study suggest that their persistent pain is not well managed. In addition to investigating the occurrence and characteristics of persistent pain in adults with SCD, future studies need to evaluate for

changes in these characteristics and evaluate the effectiveness of different analgesic regimens to improve pain management and functional status in this vulnerable population.

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Table 1. Demographics and Clinical Characteristics for the Total Sample and Differences Between the Pain Groups

Characteristics	Total Sample (n = 94) Mean (SD)	Manageable Pain (n = 66) Mean (SD)	Unmanageable Pain (n = 28) Mean (SD)	p-value
Age (years)	36.7 (13.1)	35.5 (13.0)	39.6 (13.2)	.18
Education (years)	13.8 (2.4)	13.9 (2.6)	13.7 (1.8)	.78
Functional status score	76.0 (15.3)	78.2 (15.1)	70.7 (14.7)	.03
SCQ Score	6.5 (3.8)	6.4 (3.8)	6.7 (3.8)	.75
	n (%)	n (%)	n (%)	
Gender				1.000
Male	31 (33.0)	22 (33.3)	9 (32.1)	
Female	63 (67.0)	44 (66.7)	19 (67.9)	
Race/ethnicity				1.000
Black/AA	90 (96.8)	63 (96.9)	27 (96.4)	
Other	3 (3.2)	2 (3.1%)	1 (3.6)	
SCD Type				.74
SS	69 (73.4)	47 (71.2)	22 (78.6)	
SC	20 (21.3)	15 (22.7)	5 (17.9)	
Sβ thalassemia	5 (5.3)	4 (6.1)	1 (3.6)	
Lives alone				
Yes	25 (27.2)	13 (20.3)	12 (42.9)	.04
No	67 (72.8)	51 (79.7)	16 (57.1)	

Marital status				.43
Never married	54 (57.4)	38 (57.6)	16 (57.1)	
Partnered	26 (27.7)	20 (30.3)	6 (21.4)	
Other	14 (14.9)	8 (12.1)	6 (21.4)	
Employment status				.33
Employed	28 (29.8)	22 (33.3)	6 (21.4)	
Unemployed	66 (70.2)	44 (66.7)	22 (78.6)	
Disabled/On disability				.01
Yes	58 (85.3)	35 (77.8)	23 (100)	
No	10 (14.7)	10 (22.2)	0 (0)	
Unemployed due to SCD				.04
Yes	55 (74.3)	35 (67.3)	20 (91.0)	
No	19 (25.7)	17 (32.7)	2 (9.1)	
Yearly income				.70
Less than $10,000	24 (27.6)	17 (28.3)	7 (25.9)	
$10,000 to $19,999	30 (34.5)	19 (31.7)	11 (40.7)	
$20,000 or higher	33 (37.9)	24 (40.0)	9 (33.3)	

Abbreviations: AA=African American, Sβ thalassemia = Sickle beta thalassemia, SC = Hemoglobin SC, SCD = Sickle cell disease, SCQ = Self Administered Comorbidity Questionnaire, SD = Standard deviation, SS = Hemoglobin SS

Table 2. Pain Characteristics for the Total Sample and Differences Between the Pain Groups

Pain Characteristics	Total sample (n =94) Mean (SD)	Manageable pain (n = 66) Mean (SD)	Unmanageable pain (n = 28) Mean (SD)	p-value
Pain now	4.1 (2.6)	3.1 (2.3)	6.6 (1.6)	<.0001
Least pain	2.5 (2.1)	1.8 (1.5)	4.2 (2.3)	<.0001
Average pain	4.2 (2.1)	3.2 (1.6)	6.6 (1.0)	<.0001
Worst pain	8.2 (2.3)	7.8 (2.6)	9.2 (1.0)	<.0001
Pain Interference (days per week)	3.7 (1.8)	3.2 (1.7)	4.8 (1.6)	<.0001
Hours per day in significant pain	10.3 (8.0)	9.4 (7.5)	12.4 (8.9)	.14
Percent pain relief from pain medicine	62.1 (26.1)	65.3 (26.1)	54.4 (25.3)	.07
Satisfaction with pain treatment	6.3 (2.5)	6.8 (2.3)	5.4 (2.6)	.02
Satisfaction with pain relief	5.6 (2.7)	6.0 (2.7)	4.6 (2.6)	.03

	n (%)	n (%)	n (%)	
Pain frequency				.002
Continuously	19 (21.1)	8 (12.9)	11 (39.3)	
At least once a day	33 (36.7)	21 (33.9)	12 (42.9)	
Several times a week	23 (25.6)	18 (29.0)	5 (17.9)	
Less than 4 times per month	15 (16.7)	15 (24.2)	0 (0.0)	
Length of time in pain				.54
Less than two weeks	23 (25.3)	16 (17.6)	52 (57.1)	
One month to one year	16 (17.6)	11 (17.5)	5 (17.9)	
More than one year	52 (57.1)	34 (54.0)	18 (64.3)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Length on time in pain (years)	21.4 (15.4)	20.4 (14.6)	23.4 (17.1)	.50

Pain Quality Assessment Scale (PQAS)

Pain Qualities	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Deep	6.5 (2.8)	5.9 (3.0)	7.9 (1.6)	<.0001
Unpleasant	6.3 (2.8)	5.5 (2.8)	8.0 (1.7)	<.0001
Throbbing	5.6 (3.0)	4.9 (3.0)	7.3 (2.2)	<.0001
Intense	5.6 (2.6)	4.7 (2.4)	7.8 (1.4)	<.0001
Aching	5.3 (3.2)	4.3 (3.2)	7.4 (2.3)	<.0001

Sharp	5.0 (3.2)	4.4 (3.2)	6.7 (2.6)	.001
Cramping	4.6 (3.1)	3.9 (3.0)	6.3 (2.6)	<.0001
Shooting	4.3 (3.0)	3.7 (2.9)	5.8 (2.9)	.002
Radiating	4.2 (3.3)	3.5 (3.2)	5.7 (3.0)	.003
Tender	4.1 (3.3)	3.6 (3.2)	5.3 (3.5)	.027
Surface	4.0 (2.8)	3.5 (2.7)	5.3 (2.7)	.005
Dull	3.7 (3.1)	3.2 (3.1)	4.8 (2.8)	.028
Heavy	3.3 (3.3)	2.7 (3.2)	4.7 (3.5)	.013
Tingling	3.1 (3.0)	2.5 (2.6)	4.7 (3.2)	.001
Sensitive	3.0 (3.2)	2.5 (3.0)	4.0 (3.5)	.034
Electrical	2.6 (3.3)	2.1 (3.0)	3.9 (3.6)	.026
Hot	2.4 (3.2)	1.6 (2.6)	4.5 (3.6)	.001
Numb	2.1 (2.9)	1.4 (2.4)	3.7 (3.4)	.003
Cold	1.6 (2.4)	1.1 (2.0)	2.8 (3.0)	.010
Itchy	1.5 (2.7)	0.9 (2.1)	3.0 (3.4)	.004

PQAS Subscale Scores

PQAS Subscales	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Paroxysmal pain	3.7 (2.3)	3.1 (2.2)	5.3 (2.0)	<.0001
Surface pain	2.3 (2.0)	1.7 (1.5)	3.6 (2.2)	<.0001
Deep/Dull pain	4.4 (2.3)	3.8 (2.2)	6.1 (1.4)	<.0001

Abbreviation: SD = standard deviation

Table 3. Pain Crisis Characteristics for the Total Sample and Differences Between the Pain Groups

Pain Crises Characteristics	Total Sample (n = 94) n (%)	Manageable Pain (n = 66) n (%)	Unmanageable Pain (n = 28) n (%)	p-value
Number of pain crises in last 12 months				1.000
0-2 times	24 (25.5)	17 (25.8)	7 (25.0)	
3-4 times	70 (74.5)	49 (74.2)	21 (75.0)	
Last pain crisis				1.000
< one month ago	49 (52.1)	34 (51.5)	15 (53.6)	
> one month ago	45 (47.9)	32 (48.5)	13 (46.4)	
Duration of last pain crisis				
< 7 days	70 (75.3)	52 (78.8)	18 (66.7)	.29
> 1 week or more	23 (24.7)	14 (21.2)	9 (33.3)	
	Mean (SD)	Mean (SD)	Mean(SD)	
Pain severity	8.1 (1.8)	8.0 (2.0)	8.4 (1.4)	.37

Table 4. Characteristics of Breakthrough Pain (BTP) in the Total Sample and Differences Between the Pain Groups

Characteristics	Total Sample (n = 85) n (%)	Manageable Pain (n = 59) n (%)	Unmanageable Pain (n = 26) n (%)	p-value
Experience BTP				.02
Yes	69 (81.2)	44 (74.6)	25 (96.2)	
No	16 (18.8)	15 (25.4)	1 (3.8)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Frequency of BTP				
Day (# times)	2.4 (1.9)	2.0 (1.5)	3.1 (2.2)	.02
Night (# times)	2.4 (2.1)	2.1 (1.6)	3.0 (2.6)	.13
Duration (minutes)	38.5 (32.6)	40.0 (33.3)	36.0 (32.0)	.63
Pain intensity	7.4 (2.1)	7.3 (2.2)	7.5 (1.8)	.70
	n (%)	n (%))	n (%)	
Location of BTP				.04
Same as usual pain	38 (44.7)	26 (44.1)	12 (46.2)	
Different than usual pain	22 (25.9)	15 (25.4)	7 (26.9)	
Both locations	10 (11.8)	4 (6.8)	6 (23.1)	
Neither location	15 (17.6)	14 (23.7)	1 (3.8)	
Predictability of BTP episodes				.10
Predictable	12 (16.7)	5 (10.9)	7 (26.9)	

Unpredictable	60 (83.3)	41 (89.1)	19 (73.1)	
Occurrence				
With movement or other activity	27 (40.3)	19 (43.2)	8 (34.8)	.60
Spontaneously	55 (80.9)	35 (79.5)	20 (83.3)	1.000
Just before next dose of pain medicine	17 (25.8)	9 (20.9)	8 (34.8)	.25
What helps your BTP?				
Take pain medication	58 (82.9)	37 (80.4)	21 (87.5)	.53
Rest	46 (67.6)	31 (68.9)	15 (65.2)	.79
Stop activity that causes the pain	28 (40.6)	19 (42.2)	9 (37.5)	.80
Other	34 (52.3)	22 (51.2)	12 (54.5)	1.000

Abbreviation: SD = Standard deviation

Table 5. Types of Prescribed Analgesic Medications for the Total Sample and Differences Between the Pain Groups

Characteristics	Total Sample n = 87 n (%)	Manageable Pain n = 61 n (%)	Unmanageable Pain n = 26 n (%)	p-value
Any analgesic prescription				1.000
Yes	76 (87.4)	53 (86.9)	23 (88.5)	
No	11 (12.6)	8 (13.1)	3 (11.5)	
Types of opioid prescriptions				.54
No opioid prescription	7 (9.0)	6 (11.1)	1 (4.2)	
Only short-acting opioid	52 (66.7)	34 (63.0)	18 (75.0)	
Only long-acting opioid	2 (2.6)	2 (3.7)	0 (0.0)	
Both short and long acting opioid	17 (21.8)	12 (22.2)	5 (20.8)	
NSAIDS	28 (32.2)	23 (37.7)	5 (19.2)	.13
Anticonvulsants	1 (1.1)	1 (1.6)	0 (0.0)	1.000
Antidepressants				N/A
TCA	0 (0.0)	0 (0.0)	0 (0.0)	
Non-TCA	0 (0.0)	0 (0.0)	0 (0.0)	

Benzodiazepines	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Muscle relaxants	1 (1.1)	1 (1.6)	0 (0.0)	1.000
Marijuana for pain	1 (1.1)	1 (1.6)	0 (0.0)	1.000

Abbreviations: NSAIDS = Non-steroidal anti-inflammatory drugs, Non-TCA = Non-tricyclic anti-depressant, SD = Standard deviation, TCA = Tricyclic anti-depressant

Chapter 4.

Pain Catastrophizing, Religiosity/Spirituality, and Quality of Life in Adults with Persistent Sickle Cell Pain

Taylor LV, Stotts NA, Humphreys J, Treadwell M, Paul S, Miaskowski C.

Pain Catastrophizing, Religiosity/Spirituality, and Quality of Life in Adults with Persistent Sickle Cell Pain

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Running Title: Coping and Quality of Life in Sickle Cell Disease

Key Words: sickle cell disease; persistent pain; pain catastrophizing; religiosity; quality of life; spirituality; chronic pain

Abstract

Persistent pain in adults with sickle cell disease (SCD) is a unique and significant problem composed of biological, psychological, social, and spiritual dimensions. A variety of strategies are utilized to cope with this disabling illness. However, little is known about the influence of biopsychosocial-spiritual factors on the quality of life (QOL) of these patients. The purposes of this study were to: compare patients with manageable and unmanageable persistent pain from SCD on catastrophizing, religiosity/spirtituality, and QOL; evaluate for associations between these factors and QOL, and determine the influence of biopsychosocial-spiritual factors on QOL of these patients. Ninety-four patients completed the Pain Catastrophizing Scale, Duke Religious Index (DRI), and Medical Outcomes Study Short Form-36 (SF-36). Cutpoints were used to divide the sample into those with manageable (average pain $\leq$5) and unmanageable pain (average pain >5). Significant correlations were found between demographic, clinical, pain, and religiosity characteristics and QOL scores. Patients with unmanageable pain were more likely to live alone, were disabled due to SCD, reported significantly lower intrinsic religiosity scores and lower SF-36 scores. Older patients with unmanageable pain and higher pain catastrophizing scores had poorer physical health. Younger patients with higher pain catastrophizing scores had poorer mental health. These findings suggest that persistent SCD pain is a significant problem, particularly for patients with unmanageable pain. More attention must be given to the biopsychosocial-spiritual factors associated with coping and persistent SCD pain and the influence of these factors on the QOL of adults with manageable and unmanageable persistent SCD pain.

Introduction

Sickle cell disease (SCD) is no longer considered a childhood disease. It is a chronic condition that poses numerous challenges for adults living with this debilitating illness.[38,48,50,54] In our recently completed cross-sectional study,[64] 93% of adults with SCD reported that they experienced persistent pain. Over half of the patients (57%) were in pain for more than one year (mean duration 21.4 (SD=15.4 years)). Of those, with persistent pain, 30% had unmanageable pain defined as an average pain intensity of >5.[77,78] Persistent pain is one of the most challenging problems encountered by adults with SCD and significantly affects their quality of life (QOL).[2,6,35,36,62]

Psychological,[19,29,65] sociological,[20,29,65] and spiritual[15,57] dimensions of pain can influence patients' experience of persistent pain. Therefore, in order to deal with the multiple dimensions of persistent pain, adults with SCD need to use of a variety of cognitive, behavioral, and spiritual coping strategies.[25,27,31,62] However, few studies have evaluated the inter-relationships among these types of coping strategies in adults with SCD who report persistent pain.[3,18, 26,54]

Catastrophizing (i.e., an orientation toward negative thinking) is a common coping strategy used by adults with pain from recurrent vaso-occlusive episodes (VOE).[3,15,36] In one study,[36] an increased number of VOEs and increased pain severity were associated with increased use of negative thinking/passive adherence. In contrast, in another study of adults with SCD,[15] while higher levels of catastrophizing were associated with poorer QOL, no associations were found between catastrophizing and pain intensity, distress, or influence. These inconsistent findings suggest that additional

research is warranted on the association between pain severity and catastrophizing in adults with persistent SCD pain.

A growing body of evidence suggests that religiosity/spirituality is an effective coping strategy for adults with persistent pain.[17,24,34,61,66] However, only six studies have evaluated the use of this coping strategy in adults with SCD.[1,7,16,26,37,46] In one study,[26] patients with higher levels of church attendance reported lower pain intensity scores and were better able to cope with their recurrent VOEs. In contrast, in two studies, while spirituality was associated with an increase in perceived control[16] and affective reactions to pain,[46] no association was found with pain severity. In one of these studies,[37] the only measure of religiosity/spirituality was the frequency of prayer. In the fourth study of adults with SCD,[1] higher levels of spirituality were associated with higher levels of self efficacy and QOL. Consistent with other research on pain in adults with SCD,[6,9,27] persistent pain was not defined in these studies. In addition, no studies were identified that evaluated for associations between religiosity/spirituality and catastrophizing in patients with manageable and unmanageable persistent SCD pain.

Persistent pain has a negative impact on the QOL of adults with SCD.[6,35] In one study that compared patients with different types of persistent pain,[6] patients with SCD reported worse scores on the Medical Outcomes Study-Short Form (SF-36) for physical functioning (PF), role-physical (RP), social functioning (SF), health perceptions (HP), mental health (MH), and bodily pain (BP) compared to patients with other persistent pain conditions. Of the eight subscales on the SF-36, PF was the most impaired area in these patients with SCD. Other studies that reported on the association between pain and QOL in adults with SCD focused on the impact of recurrent VOEs[58] or did not provide detailed

information on the pain problem.[35,76] Therefore, little is known about the impact of persistent SCD pain on these patients' QOL.

Taken together, findings from these studies suggest that a multidimensional evaluation of persistent pain in adults with SCD is needed to better understand the coping strategies that they use, as well as the influence of biopsychosocial-spiritual factors on their QOL. While findings from several studies suggest that a significant number of patients with SCD experience unmanageable pain and catastrophize over their pain,[3,15,18,36] no studies have compared the use of psychological and religious/spiritual coping strategies in patients with manageable and unmanageable persistent SCD pain. In addition, no studies have investigated the association between religiosity/spirituality and pain catastrophizing. Therefore, building on our previous study,[64] the purposes of this study in a sample of patients with manageable (average pain intensity ≤5) and unmanageable (average pain intensity >5) persistent pain from SCD were to: evaluate for between group differences in pain catastrophizing, religiosity/spirtituality, and QOL and determine the effects of selected demographic (e.g., age, gender, living arrangement, employment status), clinical (e.g., comorbidity, functional status), pain (e.g., pain group membership, pain severity, experience of breakthrough pain (BTP)), psychological (e.g., catastrophizing), and religious/spiritual characteristics on QOL (i.e., physical and mental health) outcomes.

Materials and Methods

Sample and Settings

This study was approved by the Committee on Human Research at the University of California San Francisco (UCSF) and the Institutional Review Board at Children's

Hospital and Research Center, Oakland (CHRCO). Informed consent was obtained from each patient.

Patients were eligible to participate if they were at least 18 years of age; had SCD and persistent pain of at least 3 months duration; had SCD, but did not have persistent pain; and were able to read and write in English. A total of 146 patients enrolled in the study. One hundred three patients completed questionnaires on pain, pain catastrophizing, religiosity/spirituality, and QOL.

Patients were recruited during clinic visits at the Adult Sickle Cell Clinic of the UCSF/San Francisco General Hospital and CHRCO; through Facebook; at San Francisco Bay Area churches, clinics, colleges, local and national SCD organizations; and through snowball sampling.

Instruments

Demographic and Clinical Characteristics

Patients provided information on gender, age, race/ethnicity, education, marital status, living arrangements, employment status, disability status, and annual income. Patients self-reported their SCD type.

Occurrence of Persistent Pain

To determine the occurrence of persistent pain, patients answered the following question: "Do you have pain and/or are you taking pain medicine or other treatments for your pain? Patients who answered "Yes" were prompted to answer additional questions about their persistent pain. Details on the pain characteristics of this sample are presented elsewhere.[64]

Pain Catastrophizing

Pain Catastrophizing Scale - Pain catastrophizing was measured with the 13 item Pain Catastrophizing Scale.[59] Items 1 through 5 were drawn from the Coping Strategies Questionnaire.[51] The remaining items were drawn from other research on catastrophic thinking in response to pain.[14,56] Patients were asked to reflect on past painful experiences and indicate the degree to which they experienced each of the 13 thoughts and feelings (e.g., I worry all the time about whether the pain will end) when experiencing sickle cell pain. Each item was rated on a five point Likert scale that ranged from 0 (not at all) to 4 (extremely). The Pain Catastrophizing Scale yields a total score and three subscale scores, which assess Rumination, Magnification, and Helplessness. A total score is computed by summing responses to all 13 items. It can range from 0 to 52. The subscale scores for the Pain Catastrophizing Scale are computed by summing the responses to specific items (i.e., Rumination = 8, 9, 10, 11, Magnification = 6, 7, 13, and Helplessness = 1, 2, 3, 4, 5, 12). The validity and reliability of the Pain Catastrophizing Scale is well established.[23,22,42,59,60] The Pain Catastrophizing Scale was used in at least one study of adults with SCD.[27] In the current study, Cronbach's alpha for the Pain Catastrophizing Scale was: Total = .93, Rumination Subscale = .86, Magnification Subscale = .72, and the Helplessness Subscale = .90.

Religiosity/Spirituality

Duke Religious Index (DRI) - Religiosity/spirituality was evaluated using the DRI, a 5-item self-report scale that was created to measure the multiple dimensions of religiosity.[33] The DRI assesses organizational or public religious activity (i.e., frequency of attendance at formal religious services), private religious activity (i.e., amount of time

spent in private religious activities), and the intrinsic (i.e., personal religious commitment) dimension of religiosity. Responses to the items on the public and private religious activity subscales are rated on a six point Likert scale (i.e., 1 = never, 2 = once a year or less, 3 = few times a year, 4 = a few times a month, 5 = once a week, 6 = several times a week). Responses to the items on the intrinsic subscale are rated on a five point Likert scale anchored by 1 (definitely not true) and 5 (definitely true). Higher scores on the DRI indicate greater religiosity. The DRI has good validity and reliability.[33,57] It was used in three studies of adults with SCD.[26,37,46] In the current study, Cronbach's alpha for the DRI Intrinsic Religiosity Subscale was .82.

QOL

Medical Outcomes Study Short Form-36 (SF-36) - QOL was evaluated using the SF-36, a generic measure of QOL, which consists of 36 items that evaluate eight domains of health status (i.e., physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH)).[70] In addition, two summary scores were calculated from the eight domain scores (i.e., physical component summary (PCS), mental component summary (MCS)) each of which has a mean of 50 and standard deviation of 10 in the United States (US) population.[71] Another item, health transition (HT), was used to measure self-reported changes in health during the past year.[69] Each of the SF-36 domain scores can range from 0 to 100 with higher scores indicating a better QOL. The SF-36 is an internationally accepted measure of QOL with well-established validity and reliability.[21,70,72-74]

Procedures

A letter of referral for eligible patients along with an Information Study Sheet was provided to the physicians and nurse practitioners at the study sites. Staff approached patients during clinic visits at both sites about participating in the study. Interested patients were referred to the researcher (LT) either in person at the clinic or by phone. In addition, patients contacted the researcher (LT) after seeing a flyer about the study.

Potential patients were screened and the study purposes and procedures were described in person or by phone. After obtaining informed consent, a total of 146 patients were enrolled in the study. Five patients were enrolled through the clinics at UCSF/SFGH and 68 patients through the clinic at CHRCO. Of these 73 patients, 74% (n=54) completed the study questionnaires. Thirty-eight patients were enrolled through the Sickle Cell Disease Foundation of California and 84% (n=32) completed the study. One patient was enrolled from a Bay Area church, six patients from conferences, four patients through Facebook, and 24 patients through snowball sampling. Of these 33 patients, 52% (n=17) completed the study questionnaires. The main reason patients did not complete the study questionnaires was illness and/or hospitalization related to their SCD.

Enrolled patients were asked to complete the study questionnaires either in paper format (n=67) or online (n=36). Patients were given approximately one week to complete the questionnaire booklet. Patients were contacted after one week by phone or e-mail if they had not completed and returned the booklet via a prepaid envelope or made arrangements to have the booklet picked up by the researcher (LT). Patients received a $20 gift card, journal, and writing pen to compensate them for completing the study questionnaires.

Data Analysis

All analyses were done using IBM Statistical Package for the Social Sciences (SPSS) Version 20.0 (Armonk, NY: IBM Corp). Based on the work of Zelman and colleagues,[77,78] using ratings of average daily pain, patients were divided into manageable (i.e., average pain ≤5) or unmanageable (i.e., average pain >5) pain groups. Descriptive statistics were used to describe the patients' demographic and clinical characteristics.

Differences in demographic and clinical characteristics between the two pain groups were analyzed using Independent Student's t-tests and Chi square analyses. The Mann-Whitney U test was used to test for differences between the two pain groups in the individual items on the DRI. Pearson product moment correlation coefficients were used to examine the relationships between the Pain Catastrophizing Scale Total, DRI, and SF-36 subscale and summary scores.

To determine which variables to include in the multiple regression analyses to predict QOL (i.e., PCS and MCS scores), correlation coefficients were calculated between the PCS and MCS scores and selected demographic, clinical, and pain characteristics, as well as catastrophizing and religiosity/spirituality scores. Multiple regression analyses were performed to determine the effects of the significant characteristics identified in the bivariate analyses on the physical and mental components of QOL. All significant variables from the bivariate analyses were entered into the model simultaneously. Variables were systematically removed to create a parsimonious model. For all tests, a p-value of <.05 was considered statistically significant.

Results

Occurrence of Pain and Categorization of Pain Groups

Ninety-four patients (91%) of the 103 who completed the study questionnaires rated their average daily pain. All remaining analyses were done with data from 94 patients. Based on ratings of average daily pain, 70% of the patients (n=66) were categorized in the manageable and 30% (n=28) were in the unmanageable pain group. Details on the differences in pain characteristics between these two pain groups are published elsewhere.[64]

Differences in Demographic and Clinical Characteristics Between the Two Pain Groups

In brief, the majority of the patients were female (67%), Black/African American (97%), had an average age of 36.6 years (range 18 – 75 years) and 13.9 (SD=2.5) years of education. Approximately 57% of patients were never married. Over half the sample (62%) had an annual income of less than $20,000/year. No differences were found between the two pain groups in gender, age, education, marital status, or income. Approximately 27% of patients lived alone. A higher percentage of patients with unmanageable pain lived alone (42.9%) compared to patients with manageable pain (20.3%; p=.04). Of the 66 patients who were unemployed, 86% were either disabled or on disability. One hundred percent of patients in the unmanageable pain group were either disabled or on disability compared to 77% of the patients in the manageable pain group (p=.02). A higher percentage of patients in the unmanageable pain group (78.6%) reported that they were unemployed due to SCD compared to those in the manageable pain group (66.7%; p=.04). Most of the patients (73%) reported having hemoglobin type SS (HbSS).

Differences in Pain Catastrophizing Scale Scores Between the Two Pain Groups

None of the Pain Catastrophizing Scale subscale and total scores differed between the manageable and unmanageable pain groups (Figure 1). For the entire sample, the total score for the Pain Catastrophizing Scale was 23.9 (SD=13.0, 59th percentile). The Rumination subscale score was 9.2 (SD=4.5, 58th percentile). The Magnification subscale score was 4.6 (SD=3.2, 65th percentile). The Helplessness subscale score was 10.0 (SD=6.6, 60th percentile). The percentile scores were derived from a study of a normative sample of injured Nova Scotia workers.[59]

Differences in DRI Scores Between the Two Pain Groups

As shown in Figure 2, no differences were found between the two pain groups on any of the DRI subscales. A comparison of the individual items on the DRI demonstrated that patients in the unmanageable pain group reported a significantly lower score for the item "I experience the presence of the Divine (i.e., God) compared to patients in the unmanageable pain group (p=.04) (Table 1).

Differences in SF-36 Scores Between the Two Pain Groups

Compared to the manageable pain group, patients in the unmanageable pain group reported significantly lower scores on PF (p=.002); RP (p=.005); and BP (p=.003) subscale scores, as well as, a significantly lower PCS (p=.001) score (Figure 3).

Regression Analyses for QOL Scores

The bivariate correlations between selected demographic, clinical, and pain characteristics, the Pain Catastrophizing Scale total and DRI subscale scores, and PCS and MCS scores from the SF-36 are summarized in Table 2. Based on the findings from these correlational analyses, a multiple regression analysis was performed to determine the predictors of PCS and MCS scores. As shown in Table 3, the overall model explained

28.1% of the variance in physical health. In terms of unique contributions, age explained 17% of the variance ($p<.001$), living alone explained 3% of the variance ($p=.08$), pain group membership explained 7% of the variance ($p=.009$), and the Pain Catastrophizing Scale total score explained 6% of the variance ($p=.01$) in physical health. Based on this analysis, older patients who were in the unmanageable pain group and those who had higher pain catastrophizing scores, reported worse physical health.

In the regression analyses for MCS scores (Table 3), the overall model explained 29.8% of the variance in mental health ($p<.001$). In terms of unique contributions, age explained 8% of the variance ($p=.005$), SCQ-13 total score explained 3% of the variance ($p=.06$), and Pain Catastrophizing Scale score explained 14% of the variance ($p<.001$) in mental health. Based on this analysis, patients who were younger and those who had higher pain catastrophizing scores reported worse mental health.

Discussion

To our knowledge, this study is the first to examine the inter-relationships among pain catastrophizing, religiosity/spirituality, and QOL in adults with persistent pain from SCD and to evaluate for differences in these dimensions between those with manageable and unmanageable pain. The original intent of this study was to evaluate for differences in the biospsychosocial-spiritual dimensions between patients with and without persistent pain. However, due to the high occurrence of persistent pain in the sample, patients were divided into manageable (70%) and unmanageable (30%) pain groups for subsequent comparisons using Zelman and colleagues' categorization.[77, 78]

Consistent with another study of adults with SCD,[15] no association was found between pain group membership and any of the pain catastrophizing scores. However,

this lack of association contrasts with previous reports that evaluated catastrophizing in patients with low back pain;[39] muscular dystrophy;[43] and fibromyalgia, spinal cord injury, and chronic whiplash.[10] In all of these studies, higher pain intensity scores were associated with higher pain catastrophizing scores. The total pain catastrophizing score in our study was higher than scores in the previous studies.[10,39,43] In addition, patients in our study scored in the 59th percentile for normative pain catastrophizing total scores compared to patients in the previous studies[10,39,43] (i.e., below the 50th percentile). Patients with pain catastrophizing total scores between the 50th and 75th percentile are at increased risk for prolonged pain and disability.[59] One consideration for the higher pain catastrophizing scores in our study compared to those in previous studies[10,39,43] may be due to racial differences between the patients in both studies. While the previous studies[10,39,43] did not report on the race of the patients, one study of patients with chronic pain[53] reported higher catastrophizing scores for African Americans compared to Caucasian patients. The fact that pain group membership was not associated with pain catastrophizing scores may be due to the length of time both groups of patients were in persistent pain from SCD.

Overall, findings from this study suggest that adults with persistent SCD pain catastrophize more than adults with other types of persistent pain. These findings may be due to the unique nature of persistent SCD pain that includes acute pain crises, frequent episodes of BTP,[64] and in many cases, life-long persistent pain,[5,8,45,47,64] as well as racial differences between patients with persistent pain.[53] More studies are needed that investigate the relationship between catastrophizing and persistent pain in adults with

SCD and that focus on strategies to prevent increased risk for persistent pain and disability in these patients.

Consistent with four studies of pain in patients with SCD,[1,7,26,37] patients in our study reported a high level of religiosity/spirituality. We hypothesized that patients with unmanageable persistent SCD pain would have lower DRI subscale scores than those with manageable pain. However, while a significant difference was found in one item of the DRI, no differences were found between the pain groups on any of the DRI subscales. These findings differ from one study of adults with pain from recurrent VOEs[26] that found that patients who attended church one or more times per week reported lower pain intensity scores. A higher proportion of the patients in the study by Harrison and colleagues[26] reported a higher frequency of church attendance (43%) and intrinsic religiosity (42%) compared to patients in our study (40% and 39%, respectively). However, in another report on the same sample,[46] patients who reported the highest frequency of church attendance reported the highest scores for their overall experience of pain (i.e., present pain index). None of the previous studies of religiosity/spirituality and pain in patients with SCD included an evaluation of persistent SCD pain.[1,7,26,37,46]

One reason why our hypothesis was not supported may be because patients with unmanageable persistent SCD pain in our study reported lower levels of physical functioning. These decrements in physical function may have prevented these patients from attending church or engaging in public religious activities, which could in turn affect the level of religious commitment in their lives (i.e., intrinsic religiosity). In fact, one study found that increased church attendance was associated with increased intrinsic religiosity (i.e., deeper level of religious commitment).[79] People may attend church for

various reasons (e.g., socialization, entertainment), but may not internalize their religious beliefs. It may be that church attendance or religious activity alone does not affect pain intensity, but rather the combination of church attendance and the level of religious commitment together may affect pain intensity in adults with persistent SCD pain. Future studies are needed to investigate the association between persistent SCD pain and religiosity/spirituality.

Consistent with previous research on QOL in adults with SCD,[3,6,35,68] all of the SF-36 subscales in this study were lower than the US population. Consistent with previous reports of patients with bone metastasis[40] and HIV,[41] patients with unmanageable persistent pain from SCD reported significantly lower PF, RP, BP, and PCS. Compared to patients with other types of persistent pain,[41,52] the PCS score for our total sample was lower. These findings suggest that physical functioning in adults with persistent SCD pain is a significant problem that warrants further research.

Interestingly, patients in our study did not report lower MH scores compared to patients with other persistent pain conditions.[12,52] The relatively normal MH scores in our sample may be related to their use of religiosity/spirituality as a coping strategy and/or increased social support (i.e., over half of the sample was married and 72% lived with someone). However, one study of patients with recurrent VOEs[3] and another study of patients with various types of persistent pain,[41] reported MH scores that were higher than patients in our study. Patients in our study reported MH scores similar to patients with persistent pain from HIV.[52]

Consistent with two studies,[4,35] several factors predicted decrements in physical health in adults with persistent SCD pain. In our study, older patients, those with

unmanageable pain, and those with higher pain catastrophizing scores had poorer physical health. Previous studies found that in addition to dealing with their pain, older adults with persistent SCD pain faced multiple challenges that impacted their QOL,[28,54] which may explain the finding in our study. In one study of younger and older adults with SCD,[28] comorbidities; unemployment due to disability; being separated, divorced, or widowed; and less tangible social support were some of the problems faced by older adults with SCD. In another study of adults with SCD, older patients, those who lived in urban areas, and those who were unemployed had poorer physical health.[4] Employment status was not associated with physical health in our study, perhaps because 70% of the patients were unemployed. Of note, the previous study [4] did not report on any pain measures.

In terms of mental health, both age and pain catastrophizing scores explained a significant portion of the variance in MCS scores. In the regression analysis for mental health, younger patients and those patients with higher catastrophizing scores had poorer mental health. This finding contrasts with another study of adults with SCD, that found no association between age and mental health.[4] One possible explanation for our findings is that older patients with persistent SCD pain may have more experience in utilizing various strategies to cope with their pain. In fact, previous research on adults with other types of persistent pain found that older patients with persistent pain utilized better coping strategies than younger patients.[43,75] Despite the fact that patients with SCD are living longer, only five studies have investigated the impact of age on QOL in adults with SCD[28-30,38,54] and only one study[54] involved patients with persistent SCD pain. More

studies are needed that investigate the impact of age on various dimensions of QOL in adults with manageable and unmanageable persistent SCD pain.

Interestingly, in our study, pain catastrophizing was a significant predictor of both physical and mental health and uniquely explained 6% of the variance in physical health and 14% of the variance in mental health. This finding is consistent with three other studies of adults with chronic fatigue syndrome and widespread pain,[44] rheumatoid arthritis,[19] and persistent somatoform pain,[49] in which higher levels of catastrophizing were associated with poorer physical and mental health. However, in one study of adults with recurrent VOEs,[36] increased catastrophizing was not associated with a reduction in physical activity. Our findings are consistent with previous research that reported that increased catastrophizing leads to increased pain intensity, which in turn may cause decreased physical ability.[60] Furthermore, patients with persistent pain may catastrophize because they feel a lack of control. Given that catastrophizing uniquely explained 14% of the variance in MCS scores, more studies are needed to explore the association between catastrophizing and physical and mental health in adults with persistent SCD pain.

Consistent with studies of adults with recurrent VOEs[3] and acute and persistent SCD pain,[35] pain group membership was not associated with MCS scores. This finding may be due to the use of religiosity/spirituality as a coping strategy, which was not measured in the previous studies. Another study reported significantly lower mental health scores in patients who were unmarried.[67] Interestingly, in that study, patients who were unmarried also reported more bodily pain. An equal number of patients were married in both pain groups in our study, which could explain the lack of association between pain marital status and mental health. Future studies need to investigate the

relationship between various coping strategies, as well as, social support and persistent SCD pain.

In contrast to one study of patients with various types of persistent pain,[13] religiosity/spirituality was not a predictor of either physical or mental health in our study. In a previous study,[13] patients who were more spiritual/religious reported significantly better scores on the PF subscale of the SF-36. It is not known if the finding in that study was due to the effects of spirituality/religiosity on physical functioning or because persons with better physical functioning were better able to engage in religious services than those with worse physical functioning. Future studies need to investigate the association between religious/spiritual health and QOL in adults with persistent pain from SCD.

Consistent with findings in other studies of adults with persistent SCD pain,[28,54,55] the majority of the patients in this study were African American, women, of low income, unemployed, and had HbSS. The majority of patients had at least one year of college. More patients with unmanageable pain lived alone, and reported that they were disabled or on disability due to SCD compared to those with manageable pain. No studies were identified that evaluated the impact of unmanageable persistent SCD pain on living arrangements in adults with SCD. However, two qualitative studies of adults with persistent pain from other medical conditions reported that persistent pain was associated with increased social isolation.[11,32] While the exact cause for the finding in our study is unknown, one possible explanation is that living arrangement could be a proxy for social support. Perhaps, patients who live with someone receive emotional, physical, and spiritual support in dealing with their pain, which facilitates better pain management and

reduced pain intensity. In terms of disability, several factors may contribute to patients with unmanageable pain being on disability compared to those with manageable pain, including, the impact of pain on physical functioning, the presence of comorbid conditions, and/or treatment-related dysfunction. More research is needed to understand the relationships between demographic and clinical characteristics and persistent pain in adults with SCD.

Several limitations need to be acknowledged. The cross-sectional design does not permit the identification of causal relationships. Longitudinal studies are needed to evaluate for changes in the relationships among pain catastrophizing, religiosity/spirituality, and QOL in adults with persistent pain from SCD. A larger sample size may help to identify differences in biopsychosocial-spiritual characteristics in patients experiencing mild versus moderate to severe persistent SCD pain. Therefore, care must be taken in generalizing the findings from this study.

With regard to evaluating religiosity/spirituality, one consideration for future research is to select instruments that take into account the limited ability of adults with unmanageable persistent SCD pain to engage in religious/spiritual activities and/or services. Selecting instruments that evaluate the unique circumstances of these patients may allow for a more in depth understanding of how religiosity/spirituality influences persistent SCD pain. In addition, while selected demographic and clinical characteristics were controlled for in our analyses, depressive symptoms that may have contributed to catastrophizing[15] were not evaluated in this sample.

Despite these limitations, this study provides evidence that adults with SCD experience manageable and unmanageable persistent pain that significantly impacts their

physical and mental health. Findings from this study represent one part of the 'pain story' of adults with persistent pain from SCD and highlight the need for the use of a biopsychosocial-spiritual model of persistent SCD pain.[63] Due to the unique etiologies and characteristics of persistent SCD pain,[5,8,45,47] adults who live with this condition on a daily basis face many challenges that require a wide range of coping strategies. More research is needed that explores the coping strategies that may yield the best possible outcomes to help patients with persistent SCD pain manage their daily pain, address the whole person, and improve their QOL.

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Figure legends

Figure 1. Differences in Duke Religious Index (DRI) religious attendance (RA), private religious activities (PRA), and intrinsic religiosity (IR) scores between patients with manageable and unmanageable persistent pain from sickle cell disease. All values are plotted as means ± standard deviations.

Figure 2. Differences in pain catastrophizing scale (PCS) total and subscale scores between patients with manageable and unmanageable persistent pain from sickle cell disease. All values are plotted as means ± standard deviations.

Figure 3. Differences in SF-36 physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), mental health (MH), self-reported health transition (HT), physical component summary (PCS), and mental component summary (MCS) between patients with manageable and unmanageable persistent pain from sickle cell disease. All values are plotted as means ± standard deviations.

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Table 1. Duke Religious Index (DRI) scores for the Total Sample and Differences Between the Pain Groups

DRI Individual Items	Total Sample (n = 93) Mean (SD)	Manageable Pain (n = 65) Mean (SD)	Unmanageable Pain (n = 28) Mean (SD)	p-value
Church/religious attendance (range 1-6)	4.0 (1.5)	4.1 (1.5)	3.8 (1.7)	.43
Private religious activities (range 1-6)	3.6 (1.7)	3.7 (1.7)	3.5 (1.8)	.53
Experience the presence of the Divine (range 1-5)	4.5 (0.9)	4.6 (0.7)	4.1 (1.1)	.04
Religious beliefs lie behind my whole approach to life (range 1-5)	4.1 (1.2)	4.1 (1.2)	4.1 (1.2)	.94
Try hard to carry religion over into all other dealings in life (range 1-5)	4.0 (1.2)	4.0 (1.1)	4.0 (1.5)	.99

Higher scores = Higher religiosity

Table 2. Relationships Between Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores on the SF-36 and Selected Demographic, Clinical, and Pain Characteristics, as well as, Pain Catastrophizing, and Religiosity/Spirituality Scores in Patients with Manageable and Unmanageable Persistent Sickle Cell Pain

	SF-36 PCS (n = 90) Total Score		SF-36 MCS (n = 90) Total Score	
Characteristics	*r*	p-value	*r*	p-value
Demographic characteristics				
Age	**-.38**	**< .001**	**.29**	**.008**
Gender-male	.13	.21	-.03	.80
Lives alone	.04	.71	-.01	.99
Employed	.05	.64	.13	.22
Clinical characteristics				
SCQ-13 score	**-.32**	**.002**	-.11	.33
KPS score	**.50**	**<.001**	**.24**	**.03**
Pain Characteristics				
BTP	-.06	.57	-.13	.24
Pain group membership	**-.29**	**.006**	-.05	.62
Pain Catastrophizing Scale total score	-.17	.11	**-.39**	**< .001**
Religiosity/Spirituality Characteristics				
DRI - Public activities	-.03	.78	.04	.72

DRI - Intrinsic	-.04	.72	.20	.07

Values in bold are statistically significant at the $p < .05$ level.
Abbreviations: BTP = breakthrough pain, DRI = Duke Religious Index, KPS = Karnofsky Performance Status score, SCQ-13 = Self Administered Comorbidity Questionnaire 13 score, SF-36 = Medical Outcomes Short Form-36

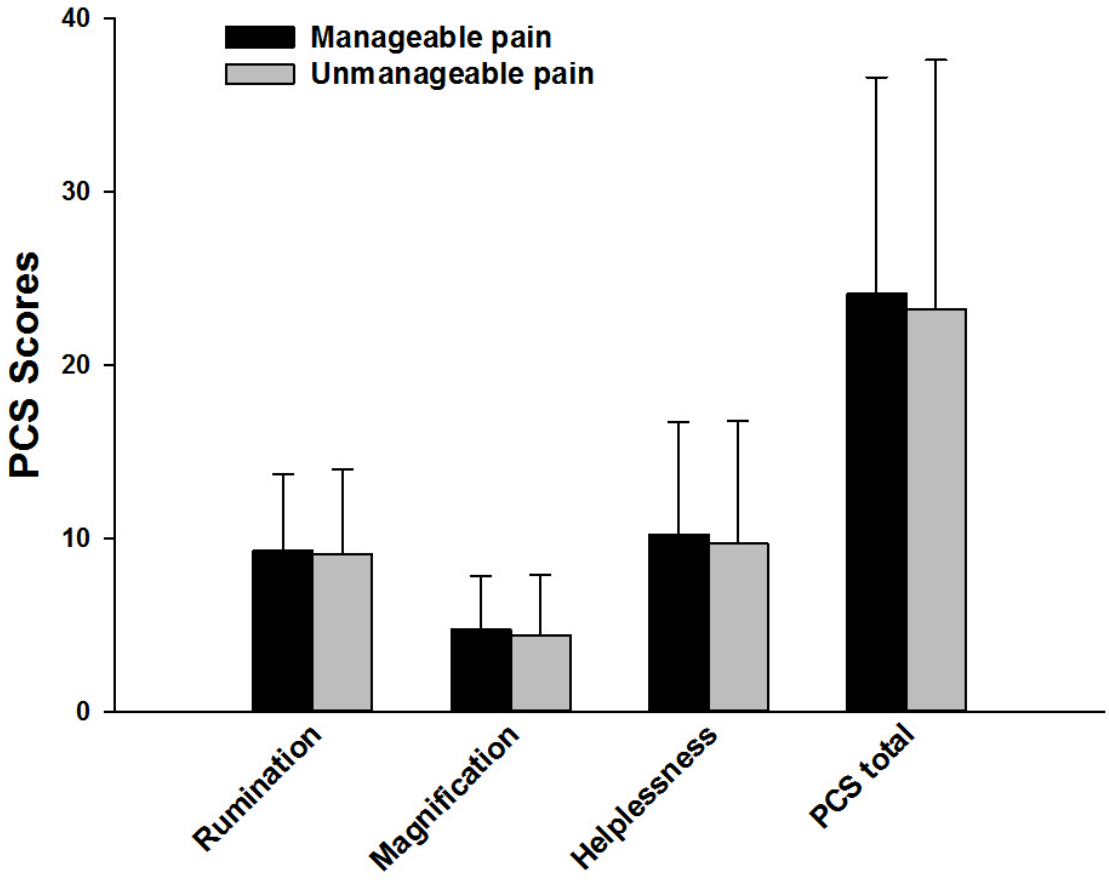
Table 3. Effect of Demographic, Clinical, and Pain Characteristics, as well as, Pain Catastrophizing on Quality of Life Outcomes of Patients with Manageable and Unmanageable Persistent Sickle Cell Pain

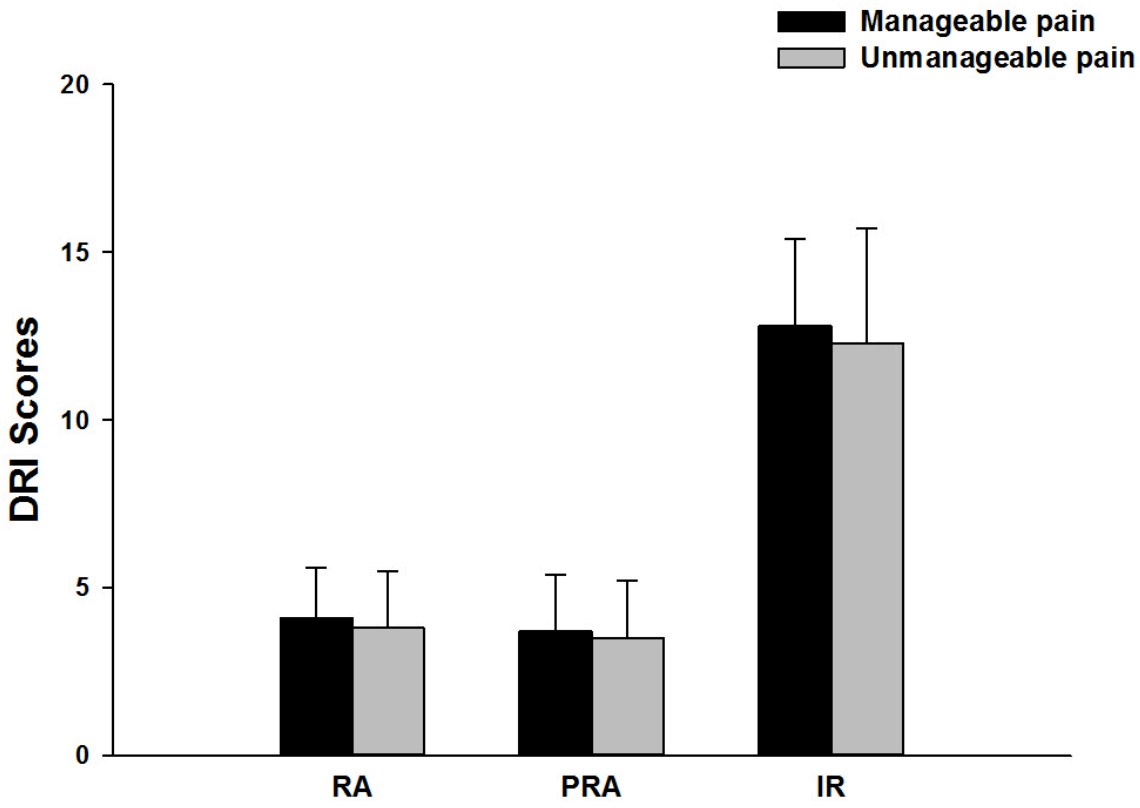
Source	R^2	*r*	β	R^2 Change	*p*
Overall Model PCS	0.281				< .001
Age (years)		-.37	-.44	.17	< .001
Lives alone		-.01	.18	.03	.079
Pain group membership		-.27	-.27	.07	.009
Catastrophizing total score		-.18	-.26	.06	.011

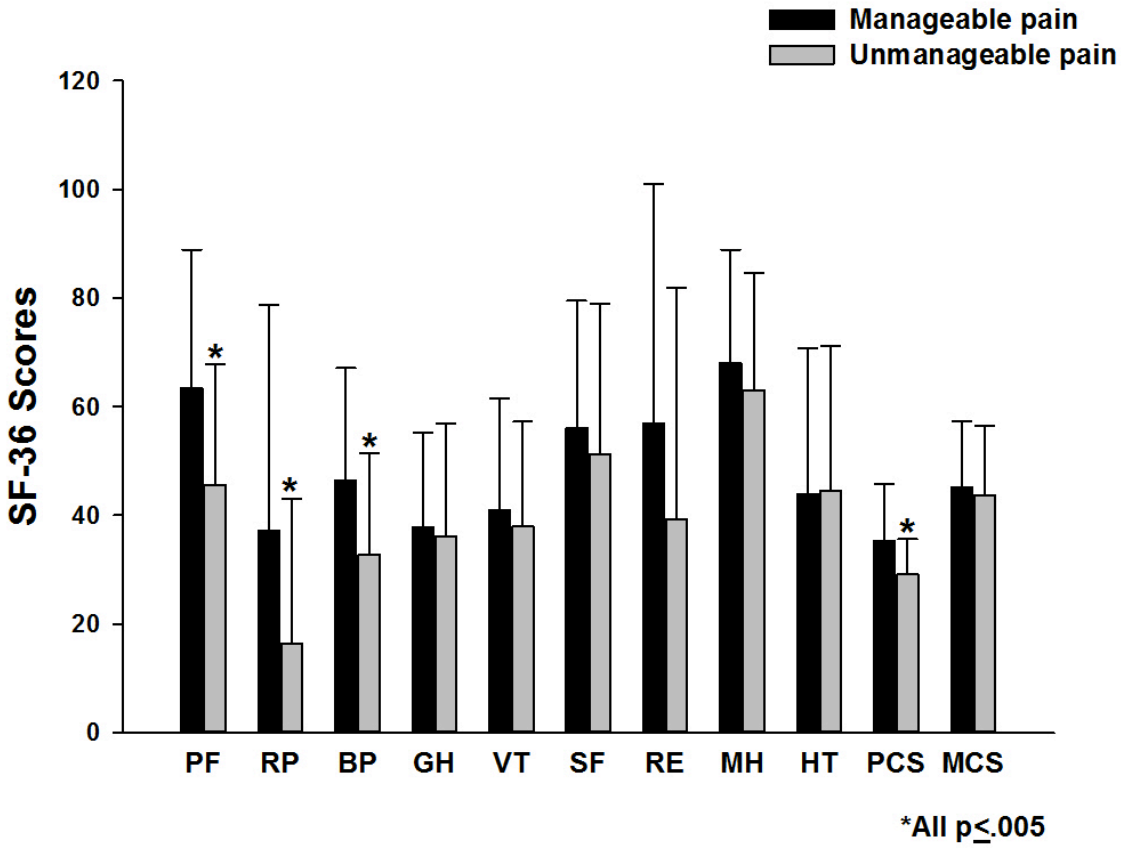
Dependent variable: Physical Component Summary (PCS) (n=82)

Source	R^2	*r*	β	R^2 Change	*p*
Overall Model MCS	.298				< .001
Age		.32	.32	.08	.005
Self-administered Comorbidity Questionnaire score		-.09	-.20	.03	.060
Pain Catastrophizing Scale score		-.46	-.38	.14	< .001

Dependent variable: Medical Component Summary (MCS) scores (n=80)


Manageable pain
Unmanageable pain
PCS Scores
40
30
20
10
0
Rumination
Magnification
Helplessness
PCS total


Manageable pain
Unmanageable pain
DRI Scores
20
15
10
5
0
RA
PRA
IR


Manageable pain
Unmanageable pain
SF-36 Scores
120
100
80
60
40
20
0
PF
RP
BP
GH
VT
SF
RE
MH
HT
PCS
MCS
*
*
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*
*All p≤.005

Chapter 5

Conclusions

The studies conducted for this dissertation address significant gaps in the literature on the occurrence and multidimensional characteristics of persistent pain in adults with sickle cell disease (SCD). The findings from this research contribute to our understanding of the differences in two common coping strategies (i.e, catastrophizing[2,4,7] religiosity/spirituality[1,3,5,6,8,9]) used by adults with manageable (average pain ≤5) and unmanageable (average pain >5) persistent SCD pain In addition, the findings from this research increase our knowledge of the biopsychosocial- spiritual factors that influence quality of life (QOL) in adults with persistent manageable and unmanageable SCD pain

Findings from this study suggest that a large number of adults with SCD experience manageable and unmanageable persistent pain, as well as, breakthrough (BTP), and simultaneous neuropathic and non-neuropathic pain that they attribute directly to their SCD and/or treatment related to their SCD. Of note, several characteristics (i.e, demographic, clinical, daily pain and BTP pain characteristics, physical functioning) experienced by adults with moderate to severe persistent pain are significantly different than those who experience mild persistent pain. In particular, we found that a significant portion of adults with unmanageable persistent pain experienced unrelieved and under-treated pain for a significant portion of their lives. In fact, we noted a disparity in prescribing practices with regard to long-acting opioids and co-analgesics compared to patients with other types of persistent pain. The average daily pain that these patients experienced is comparable to that experienced during a vaso-occlusive episode (VOE). Furthermore, unmanageable persistent pain was associated with decrements in

physical and mental health and has negative effects on social functioning and spiritual health.

Findings from our study suggest that the overall QOL of adults with persistent SCD pain is lower than the general population. The most substantial impact on QOL in these patients is attributed to the impact of unmanageable pain on physical functioning. In addition, age and the strategies that these adults utilized to cope with their pain may impact their QOL. In particular, findings from this study suggest that patients with manageable and unmanageable persistent SCD pain catastrophize about their pain more than patients with other types of persistent pain. Interestingly, catastrophizing was associated with decrements in both physical and mental health in patients with persistent SCD pain.

Implications for Clinical Practice

A multidimensional evaluation (e.g., cause(s) of persistent pain, pain qualities, assessment of BTP, pain relief, religious/spiritual and psychological coping, impact of persistent pain on age, physical and mental health, impact of social support) of pain may help clinicians to identify the biopsychosocial-spiritual factors that are associated with persistent pain in adults with SCD. In particular, this type of evaluation will undoubtedly prove most effective for adults who experience unmanageable persistent pain on a daily basis. In addressing the challenges of managing persistent SCD pain, prescribing medications that are effective in relieving pain in patients with other types of persistent pain, may help to relieve pain in patients with persistent SCD pain. Furthermore, it may help to narrow the gap that exists in prescribing practices between patients with persistent SCD pain and patients with other types of persistent pain.

Clinicians need to keep in mind that treatment modalities and resources aimed at helping younger, as well as, older adults cope with their pain may improve QOL in adults with persistent SCD pain. Overall, multidisciplinary management of persistent pain has implications for decreased healthcare costs, improved pain management and outcomes, as well as improved QOL in adults with manageable and unmanageable persistent pain.

Directions for Future Research

Future studies need to include larger sample sizes to identify differences in biospsychosocial-spiritual factors between those with manageable and unmanageable persistent SCD pain. Larger sample sizes may identify additional factors that predict QOL outcomes in these adults. In addition, longitudinal studies are needed to identify which characteristics of persistent SCD pain change over time.

Future research needs to evaluate the impact of BTP on the persistent pain experience of adults with SCD. Since findings from this study suggest that BTP is a significant daily occurrence in the lives of adults with SCD, future research is needed to determine differences between BTP, VOEs and daily persistent pain in adults with manageable and unmanageable persistent SCD pain. Studies are needed that evaluate the pain characteristics associated with BTP (e.g., pain qualities, pain behavior, pain interference) in adults with persistent SCD pain, particularly patients with unmanageable persistent pain.

More studies are needed to evaluate the analgesic and co-analgesic medications prescribed to adults with persistent manageable and unmanageable persistent SCD pain. Future studies need identify the doses prescribed and taken by these adults, as well as, the effectiveness of these analgesics on BTP and daily persistent pain. In addition, more

studies are needed that evaluate the use and effectiveness of prescribed marijuana for persistent manageable and unmanageable SCD pain. Studies that compare effectively prescribed analgesic medications for adults with other types of persistent pain to those prescribed for patients with persistent SCD pain are needed to evaluate for improvements in pain relief in adults with SCD.

More studies are needed to evaluate the impact of age on manageable and unmanageable persistent SCD pain in adults. Studies are needed to compare coping strategies utilized by younger and older adults with SCD and how these coping strategies impact the experience of persistent pain.

Finally, future research should focus on the multidimensional nature of persistent SCD pain. Future studies are needed that evaluate the impact of biopsychosocial-spiritual factors on persistent SCD pain. More studies are needed to understand the impact of religiosity/spirituality on persistent pain in these adults and evaluate differences in these factors between adults with other types of persistent pain. Particular attention should be given to adults with unmanageable persistent SCD pain and how these factors are related to their ability to cope with their pain and influence their QOL.

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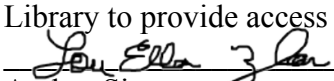

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