

Non-Pharmacological Approaches for Pain Management in Sickle Cell Disease:

Development of a Mindfulness-Based Intervention

by

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Dissertation submitted in partial fulfillment of  
the requirements for the degree of Doctor  
of Philosophy in  
Nursing in the Graduate School  
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2016

ABSTRACT

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## **Abstract**

**Background:** Sickle Cell Disease (SCD) is a genetic hematological disorder that affects more than 7 million people globally (NHLBI, 2009). It is estimated that 50% of adults with SCD experience pain on most days, with 1/3 experiencing chronic pain daily (Smith et al., 2008). Persons with SCD also experience higher levels of pain catastrophizing (feelings of helplessness, pain rumination and magnification) than other chronic pain conditions, which is associated with increases in pain intensity, pain behavior, analgesic consumption, frequency and duration of hospital visits, and with reduced daily activities (Sullivan, Bishop, & Pivik, 1995; Keefe et al., 2000; Gil et al., 1992 & 1993). Therefore effective interventions are needed that can successfully be used manage pain and pain-related outcomes (e.g., pain catastrophizing) in persons with SCD.

A review of the literature demonstrated limited information regarding the feasibility and efficacy of non-pharmacological approaches for pain in persons with SCD, finding an average effect size of .33 on pain reduction across measurable non-pharmacological studies. Second, a prospective study on persons with SCD that received care for a vaso-occlusive crisis (VOC; N = 95) found: (1) high levels of patient reported depression (29%) and anxiety (34%), and (2) that unemployment was significantly associated with increased frequency of acute care encounters and hospital admissions per person.

Research suggests that one promising category of non-pharmacological interventions for managing both physical and affective components of pain are

Mindfulness-based Interventions (MBIs; Thompson et al., 2010; Cox et al., 2013). The primary goal of this dissertation was thus to develop and test the feasibility, acceptability, and efficacy of a telephonic MBI for pain catastrophizing in persons with SCD and chronic pain.

**Methods:** First, a telephonic MBI was developed through an informal process that involved iterative feedback from patients, clinical experts in SCD and pain management, social workers, psychologists, and mindfulness clinicians. Through this process, relevant topics and skills were selected to adapt in each MBI session. Second, a pilot randomized controlled trial was conducted to test the feasibility, acceptability, and efficacy of the telephonic MBI for pain catastrophizing in persons with SCD and chronic pain.

Acceptability and feasibility were determined by assessment of recruitment, attrition, dropout, and refusal rates (including refusal reasons), along with semi-structured interviews with nine randomly selected patients at the end of study. Participants completed assessments at baseline, Week 1, 3, and 6 to assess efficacy of the intervention on decreasing pain catastrophizing and other pain-related outcomes.

**Results:** A telephonic MBI is feasible and acceptable for persons with SCD and chronic pain. Seventy-eight patients with SCD and chronic pain were approached, and 76% (N = 60) were enrolled and randomized. The MBI attendance rate, approximately 57% of participants completing at least four mindfulness sessions, was deemed acceptable, and participants that received the telephonic MBI described it as acceptable, easy to access, and consume in post-intervention interviews. The amount of missing data

was undesirable (MBI condition, 40%; control condition, 25%), but fell within the range of expected missing outcome data for a RCT with multiple follow-up assessments.

Efficacy of the MBI on pain catastrophizing could not be determined due to small sample size and degree of missing data, but trajectory analyses conducted for the MBI condition only trended in the right direction and pain catastrophizing approached statistical significance.

**Conclusion:** Overall results showed that a telephonic group-based MBI is acceptable and feasible for persons with SCD and chronic pain. Though the study was not able to determine treatment efficacy nor powered to detect a statistically significant difference between conditions, participants (1) described the intervention as acceptable, and (2) the observed effect sizes for the MBI condition demonstrated large effects of the MBI on pain catastrophizing, mental health, and physical health. Replication of this MBI study with a larger sample size, active control group, and additional assessments at the end of each week (e.g., Week 1 through Week 6) is needed to determine treatment efficacy. Many lessons were learned that will guide the development of future studies including which MBI strategies were most helpful, methods to encourage continued participation, and how to improve data capture.

## **Dedication**

I dedicate this dissertation to the patients of the Comprehensive Adult Sickle Cell Center at Duke University.

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# **1. Chapter 1 - Introduction**

## ***1.1 Problem and Introduction***

Pain is the hallmark symptom of sickle cell disease (SCD). It is estimated that 50% of adults with SCD experience pain on most days, and 1/3 experience chronic pain (Smith et al., 2008). Persons with SCD and chronic pain have worse physical and emotional health (Booker et al., 2006), and have higher hospitalization rates, doctor visits, non-crisis pain episodes, and overall higher utilization of healthcare services than those with low levels of anxiety, depression, and stress (Sogutlu, 2011).

Therefore leaders in pain management recommend integration of biological, behavioral, and social interventions to treat chronic pain. The importance of pharmacotherapy for pain in SCD, primarily opioids, has been recognized over the past three decades; however, the use of non-pharmacological strategies to help cope with and manage chronic pain related to SCD has received little attention. It is also generally recognized that pharmacologic interventions alone are rarely sufficient, and because of the recent increase in unintentional deaths from opioids, it is highly desirable to incorporate non-pharmacologic approaches to manage pain (CDC, 2016).

## ***1.2 Background***

### **1.2.1 Epidemiology**

SCD is a life threatening condition that affects more than 7 million people world wide (NHLBI, 2014). In the United States one out of every 375 African Americans is affected by sickle cell disease (SCD; Edwards et al., 2005), making SCD the most

common genetic hematological disorder in the United States. SCD primarily affects African Americans and those of Caribbean descent, but is still found in Caucasians from southern Europe and the Mediterranean, and in people from the Middle East and India (El-Hazmi, Al-Hazmi, & Warsy, 2011). In the early 1980s the average lifespan for men and women with SCD in the United States was between 42 and 48 years, respectively (Platt et al., 1994), but more recently the overall mortality rate has increased by 1% each year since 1979 with the median age of death now being 42 for females and 38 for males (Lanzkron, Carroll, & Haywood, 2013).

### **1.2.2 Physiology and Genetics**

Unlike any other genetic hematological disease, red blood cells produced by the body in SCD have a sickled or crescent shape. The abnormal shape of these cells, caused by a defective hemoglobin protein, inhibits red blood cells from being able to adequately carry oxygen during conditions of stress (Bensinger & Gillette, 1974). When red blood cells are unable to carry oxygen they become dehydrated, systemic inflammatory reactions occur, along with abnormalities of cellular adhesion and vascular tone (Odievre et al., 2011) often leading to hemolysis. These physiological changes result in numerous physical complications that over time produce multi-system organ failure and eventually death.

The extent of these pathological changes and resulting complications is largely based on the type of inherited hemoglobin genotype and individual differences (Bonner, Puffer, & Willard, 2010). The term sickle cell disease (SCD) is typically used to describe

all conditions associated with sickling of red blood cells, whereas the term sickle cell anemia is generally used to describe homozygosity for Hemoglobin S (ie., Hb S). In the United States, the most prevalent genotype, HbS, and less common HbSB<sup>0</sup> thalassemia, are both commonly referred to as sickle cell anemia (SCA) because they are associated with the most severe clinical manifestations (Yawn, et al 2014). Other variations of SCD in the United States include hemoglobin SC disease (Hb SC), and hemoglobin S-beta thalassemia<sup>+</sup>.

Typically the disorder is most severe in persons with homozygosity for HbSS, intermediate severity in hemoglobin SC (HbSC, combined hemoglobins S and C), and generally benign in those with sickle cell trait (HbAS) (Bonner, Puffer, & Willard, 2010). For instance, persons with sickle cell anemia (e.g., HbSS, SB<sup>0</sup>) are more likely to experience the most severe complications and have the highest re-hospitalization rates than other types (e.g., HbSC, HbE) (Lorey, Arnopp, & Cunningham, 1996; Brousseau et al., 2010), and have a younger median age of death than persons without sickle cell anemia (Platt et al., 1994). But it is important to note that this is not true for all patients, and some patients may experience symptoms and complications related to SCD regardless of the specific genotype. Additionally individuals with the same genotype can experience complications earlier or later in life compared to others with the same genetic malformation.

## **1.2.3 Complications**

### **1.2.3.1 Biological Complications**

Persons with SCD can suffer from many complications that may include, but are not limited to chronic anemia, stroke, acute chest syndrome, avascular necrosis, blindness, pulmonary embolus, pneumonia, renal failure, gallbladder and liver disease, iron overload, retinopathy, and many other serious complications (John, 2010; Cluster & Vichinsky, 2003). Signs and symptoms of these physical complications can start at a very young age. It is not uncommon for persons with SCD to have had an arthroplastic procedure (e.g., hip replacement) before the age of 30 (Acurio & Friedman, 1992; Al-Mousawi et al., 2002). In one study the youngest patient to present with avascular necrosis of the hip was 6 years old (Adekile et al., 2001).

The most common complication experienced by persons living with SCD, at some point in their life, is pain. In one study of persons with homozygous sickle cell (HbSS), 50% of the 302 children became symptomatic before the age of two, and an acute episode of pain was the initial symptom in 25% and the most frequent symptom after the age of two (Bainbridge et al., 1985). Persons with SCD experience both acute and chronic pain, but most healthcare providers associate sickle cell pain with the acute pain referred as a vaso-occlusive crises (VOC).

Vaso-occlusive crises (VOC) are a unique type of pain found only in persons with SCD, caused by an accumulation of sickled red blood cells in the vasculature resulting in damage (acute pain) to the surrounding tissue areas (Powars et al., 2005). Each VOC is

unique in that it can last for minutes, hours or days, and differ between previous VOC's in terms of severity, location, and frequency (NHLBI, 2014). In general VOC's are described as sudden onset, unpredictable, debilitating and excruciating.

VOC often necessitates treatment in an emergency department setting, although some patients are able to treat the pain at home with pharmacologic approaches, often augmented by non-pharmacologic techniques. For persons with SCD, VOC's account for approximately 76.9% of all acute hospitalizations and 64.2% of emergency department visits (Brousseau et al., 2010). Persons with SCD rarely seek healthcare for these crises (3.5%), which may mean health care providers greatly underestimate the number of crises that occur in their SCD patients (Smith et al., 2008).

Persons with SCD are often aware of specific factors that can provoke a VOC, although often not able to fully control these factors. Modifiable factors that a patient has some control over include dehydration, low environmental temperature, extreme physical exercise or physical stress, and alcohol, other factors (e.g., active infection) the patient has little control over but can also provoke a VOC (Yale, Nagib, & Guthrie, 2000).

Hydroxyurea is the only approved drug by the FDA for the treatment of SCD is hydroxyurea (HU; Charache et al., 1997) and can reduce the occurrence of VOC. and prevent other medical complications. A number of longitudinal and multisite studies have demonstrated hydroxyurea is effective in reducing the frequency of painful events and acute chest syndrome, the number of needed blood transfusions, and can decrease mortality related to disease progression (Segal et al., 2008).

In addition to VOC, persons with SCD can experience chronic pain, defined by the American Psychological Association, as “pain that lasts longer than six months and affects how a person lives their daily life” (“Coping with Chronic Pain”, n.d.). Recent work has shown that when looking at all types of pain experienced by persons with SCD, chronic pain is experienced at a much higher rate than pain from VOC's. The Pain in Sickle Cell Epidemiological Study (PiSCES), a landmark study that investigated sickle cell pain, found that adults reported chronic pain at home 38% of the time, versus only 12.7% VOC pain, of the 31,000 days surveyed (Smith et al., 2008).

In a report released by the National Heart, Lung, and Blood Institute, *Evidence-Based Management of Sickle Cell Disease* (NHLBI, 2014), chronic pain is divided into four categories: chronic pain of unclear etiology, chronic pain related to an objective cause, chronic neuropathic pain, and “breakthrough” pain. Chronic pain of unclear etiology can be an extension of recurrent acute pain episode, while chronic pain related to an objective cause is due to specific tissue or organ damage (e.g., avascular necrosis of hips, leg ulcers). Chronic neuropathic pain can be secondary to peripheral or central nerve injury or dysfunction and is typically due to damage caused by occluded blood vessels (e.g., mental nerve neuropathy, spinal cord infarction), versus breakthrough pain which is a flair-up of sudden pain that is unresponsive to usual therapy (no data that clearly describes or defines break-through pain at this point) (Ballas, 2011).

Regardless of its origin, quality of life is dramatically hindered by chronic pain. Chronic pain decreases social functioning, food consumption, physical activity, and

mobility in persons with SCD (McClish et al., 2005; Pells et al., 2005; Smith et al., 2005; Sadat-Ali, 1993). Increases in chronic pain have also been associated with recurrent emotions of fear, uselessness, helplessness, and worsening of physical and emotional health (Booker et al., 2006).

### **1.2.3.2 Behavioral Complications**

Persons with SCD can experience a variety of behavioral complications. For instance, depression and anxiety among individuals with SCD ranges from 2% to 57% (Levenson et al., 2008; Jonassaint et al., 2016), and is often exacerbated by SCDs chronicity and unpredictable pain crises (Molock & Belgrave, 1994). This is of concern because persons with SCD and high levels of depression or anxiety have more frequent pain episodes, higher hospitalization rates, doctor visits, and overall higher utilization of healthcare services (Levenson, et al. 2008).

To manage challenges related to depression and anxiety, persons with SCD report using negative coping skills, such as avoidance to manage feelings of depression and anxiety (Citero et al., 2007; Booker et al., 2006). But the use of negative coping strategies such as avoidance (e.g., suppressing undesirable cognitions and emotions) may increase the number of ED visits or hospital admissions, and perpetuate misuse of prescribed opioids (Garland, Brown, & Howard, 2016).

Pain catastrophizing is an important factor associated with behavioral health and chronic pain management for persons with SCD (Citero et al., 2007). Pain catastrophizing is a negative mental state toward pain stimuli and pain experience that

can exacerbate chronic pain (Vowles, McCracken, & Eccleston, 2008). Individuals who catastrophize tend to ruminate, experience feelings of helplessness, and magnify expected or actual pain stimuli (Quartana, Campbell, & Edwards, 2009). Pain catastrophizing is associated with increases in pain intensity, pain behavior, analgesic consumption, frequency and duration of hospital visits, and with reduced daily activities (Sullivan, Bishop, & Pivik, 1995; Keefe et al., 2000; Jacobsen & Butler, 1996; Be'dard et al., 1997; Gil et al., 1992; Gil et al., 1993; Keefe et al., 1989).

Compared to other chronic pain populations (e.g., rheumatoid arthritis and spinal cord injury), SCD patients have higher levels of catastrophizing (Citero et al., 2007). Catastrophizing in SCD patients has also been associated with increased pain severity, pain sensitivity, bodily pain, and pain frequency (Gil et al., 1989; Gil et al., 1995; Citero et al., 2007; McCrae & Lumley, 1998). In addition to increasing the severity of chronic pain, catastrophizing also increases the interference that chronic pain has on quality of life. Patients that catastrophize report decreased social functioning, mental health, and increased depression severity and work absences (Citero et al., 2007; Gil et al., 2004).

### **1.2.3.3 Social Complications**

Many persons with SCD experience a diverse range of social complications. Children with SCD face issues related to 'adjustment' domains (e.g., illness, social, academic, psychological, and family adjustment) that are often not recognized by social workers, schoolteachers, or healthcare professionals (Barbarin, Whitten, Charles, et al. 1994). Adult challenges include occupational disability, transportation, stable social

relationships, drug dependency, and significant medical expenses (Bulter & Beltran, 1993; Pettignano, Caley, & Bliss, 2011).

In a study of a SCD support group (Bulter & Beltran, 1993), patients reported that they: (1) had difficulty fulfilling an occupational role because of life-long patterns of disruption from SCD, and that because they are “work capable” during non-crisis periods they are not automatically eligible for disability benefits, (2) their pain crises often create “disequilibrium” in relationships with their significant others, often placing their spouse or partner in a position of taking over their responsibilities, and (3) are afraid of becoming dependent on pain medications and being viewed as “manipulative” by physicians or nurses when they describe which medications work best for them.

Persons with SCD also report poor interpersonal treatment and discrimination within health-care settings. Discrimination by healthcare providers has been correlated with greater clinical pain severity and sensitivity to pain, increased stress and depression, and decreased sleep in persons with SCD (Mathur et al., 2016). Experiences of discrimination in the healthcare system have also been correlated with treatment non-adherence and lack of self-care by persons with SCD, greater burden of pain, increased hospital admissions and ED visits, and duration of hospitalizations for pain crises (Haywood et al., 2014; Stanton et al., 2010).

In general most social complications are closely correlated with low socio-economic status (SES; Wiltshire et al., 2009; Heck & Parker, 2002). Low SES affects approximately 67.24% of persons with SCD (Swarnkar, Kale, & Lakhkar, 2010). Persons

with SCD who have low SES experience longer hospital length of stay (McCavit et al., 2011), decreased hemoglobin concentration and anthropometric attainment (Animasahun et al. 2011), increased primary teeth decay and number of teeth extracted (Luna et al., 2012) and increased bone pain crises and leg ulcerations (Okany & Akinyanju, 1993).

The effects of low SES are often experienced at young age and exacerbate healthcare-related stigma and continue into young adulthood (Jenerette & Brewer, 2011). Persons with SCD and low SES have diminished quality of life (Panepinto et al., 2008), and the quality of life for caregivers of children with SCD is also decreased (van den Tweel et al., 2008). Low SES is also more prevalent among minorities (e.g., African Americans), who often experience greater psychological stress and lack of control over their lives due to inadequate social support, often predisposing them to legal issues as well (Alder & Conner-Snibble, 2003; Pettigano, Caley, & Bliss, 2011).

There are a number of potential reasons for why these unmet social needs exist for persons with SCD, but at this time there is very little evidence to support any one specific reason. One assumption is due to the lack of financial resources to pay for medical expenses. Prior to the passage of the Affordable Care Act (ACA), insurance companies commonly denied coverage to persons with chronic or pre-existing conditions, such as those with SCD, making it extremely difficult to pay for medical expenses. In addition, lifetime caps on coverage by insurance companies have also limited the amount of care that could be received, and not all patients with SCD are eligible for disability benefits

and government sponsored health services to help pay for treatment (Social Security Disability, 2016).

A second, closely related reason is due to low SES and co-morbid behavioral complications. Numerous studies have demonstrated strong associations between low socioeconomic status with race/ethnicity status and access to care (Shi & Stevens, 2005). Persons with low SES do not have the same resources available as persons in the middle and upper SES categories. Depression or anxiety, which are common among persons with low SES (Sherbourne et al., 2001), can also make it more difficult to seek help for their social needs. Approximately two-thirds of people with depression and anxiety do not seek treatment, and only about 50% of patients with depression are recognized by their primarily health care provider and receive additional psychosocial services (Regier et al., 1993, González et al., 2010).

But regardless of how these unmet social needs arise, their presence can contribute to negative biological and behavioral health outcomes for persons with SCD.

#### **1.2.4 Treatments for Chronic Pain**

Treatments for chronic pain in SCD are not aimed at curing the pain but at reducing pain interference and improving function. Chronic pain treatments for persons with SCD can be broadly categorized as either pharmacological or non-pharmacological. This discussion focuses on *current* pharmacological and non-pharmacological treatments for chronic pain in SCD.

#### **1.2.4.1 Pharmacological Treatments for Chronic Pain**

At this time there is no nationally standardized pharmacological regimen for the treatment of chronic pain for persons with SCD, there are only recommendations as to what there is high quality for and low quality clinical evidence for (NHLBI SCD, 2014). Despite not having a standardized treatment regimen to follow healthcare providers typically prescribe long-term opioid therapy for chronic pain in SCD. It is estimated that of the 55% of persons with SCD and chronic pain, approximately 78% use long or short-acting opioids to manage their pain despite a lack of evidence for its long-term use (Smith et al., 2008 & 2015; Warner, 2012).

There are many concerns associated with using chronic opioids for the treatment of chronic, non-cancer pain. These risks include: (1) the increasing unintentional drug overdose rates resulting in unintentional deaths (CDC 2016), and (2) lack of evidence for long-term opioid use in chronic non-cancer pain patients (Warner, 2012). A recent meta-analysis on the quality of life for long-term opioid users with chronic non-cancer pain by Chou and colleagues (2015) found insufficient evidence to conclude that opioids improve quality of life or provide significant functional improvements. In addition, chronic opioid therapy only addresses the sensory and physical dimension of pain and does not address the affective, behavioral, cognitive, cultural, or social dimensions of chronic pain (Savage et al., 2003). It is therefore important to examine possible non-pharmacologic approaches to managing chronic pain in SCD.

#### **1.2.4.2 Non-Pharmacological Treatments for Chronic Pain and Application to SCD**

A variety of non-pharmacological interventions have been used for persons with chronic pain. Non-pharmacological interventions are typically categorized as either physical or psychosocial, and based on one of four psychological models: operant, peripheral physiological, cognitive and coping, or central neurophysiological (Jensen & Turk, 2014).

Although the efficacy of non-pharmacological therapies for persons with SCD has not been studied to the same extent as pharmacological therapies, the literature does support the use of non-pharmacological therapies (Hildenbrand, et al., 2014; Sansom-Daly, et al., 2012; Edwards et al., 2010), particularly in conjunction with pharmacological treatments. For example, one study found that combining cognitive behavioral therapy (CBT) with hydroxyurea, used to prevent VOC, is more effective than hydroxyurea alone in improving patient quality of life and coping ability (Cummins & Anie, 2003).

Even though research does exist that supports the use of non-pharmacological therapies for persons with SCD, very little evidence has been gathered on the use of non-pharmacological interventions to decrease pain or pain catastrophizing in persons with SCD (Anie & Green, 2012; NHLBI, 2014). Despite a lack of evidence for efficacy of non-pharmacological intervention use in persons with SCD, non-pharmacological treatments are increasingly considered as part of the standard of care for persons with SCD (Edwards & Edwards, 2010). For example in the SCD guidelines produced by the National Heart, Lung, and Blood Institute (NHLBI, 2014), non-pharmacological

recommendations are made (e.g., deep tissue/massage therapy, muscle relaxation therapy) despite a lack of strong evidence to support their efficacy in SCD.

Lastly, as described in the behavioral health section, chronic pain can be exacerbated by pain catastrophizing. Yet despite the literature showing how important it is to reduce pain catastrophizing in persons with chronic pain, no clinical studies have been conducted to identify effective interventions that may reduce catastrophizing and subsequently improve quality of life in persons with SCD. Given the significant negative effects of catastrophizing in SCD patients, and the paucity of research, there is need to test interventions aimed at reducing pain and pain catastrophizing among persons with SCD living with chronic pain.

#### **1.2.4.3 Mindfulness-based Interventions**

A promising category of non-pharmacological interventions for managing both physical and affective components of pain are Mindfulness-Based Interventions (MBIs) (Thompson et al., 2010; Cox et al., 2013).

There is strong evidence to support the use of MBIs for persons suffering from chronic pain. Mindfulness-based interventions teach patients that sensing pain, even if it is intense or chronic, does not need to be fought, ignored, suppressed, or inhibit them from living a meaningful life or accomplishing their goals (Vowles, McCracken, & Eccleston, 2008). This approach challenges patients to decrease pain-related cognitive and emotional reactivity that can increase distress and exacerbate pain (e.g., pain catastrophizing), and to engage in active coping of the present moment (Kabat-Zinn,

Lipworth, & Burney, 1985). Multiple systematic and Cochrane reviews on the utility of MBIs for pain and pain coping have been published, which largely support the use of MBIs (Veehof et al., 2011).

The practice of acceptance within MBIs make it a well-suited intervention for reducing pain catastrophizing because MBIs fundamental approaches (acceptance, non-judgmental awareness, and presence of the current moment) are diametrically opposed to the core elements of pain catastrophizing (rumination, helplessness, and pain magnification). Patients who catastrophize pay heightened attention to painful bodily sensations and experience more negative mental states and judgments towards pain, while mindfulness teaches patients to monitor all painful bodily sensations, without judgment, and accept them for what they are. In non-SCD samples, the use of mindfulness techniques has been found to be inversely correlated to pain catastrophizing, physical disability, depression, pain-related anxiety, and psycho-social disability (Vowles, McCracken, & Eccleston, 2008; Dahl, Wilson, & Nilsson, 2004; Kratz, Davis, & Zautra, 2008).

There are also several key elements of a MBI that make it ideal for persons with SCD. First, MBIs have been applied within a variety of acute and chronic pain populations (Rosenzweig et al., 2010; Grossman, et al. 2007), and have been used to manage symptoms from other non-pain chronic diseases that affect African American's such as hypertension, type 2 diabetes, and HIV/AIDS (Hughes et al., 2013; Miller et al. 2013; Robinson, Matthews, & Witek-Janusek, 2003). Second, MBIs can be delivered remotely in the home; many persons with SCD experience transportation challenges

(Gardner-Nix et al., 2008; Bazarko et al., 2013; Smith et al., 2005; Levenson et al., 2008). Third, MBIs are free of cultural and religious beliefs; many persons with SCD in the United States are African American and report a formal religious affiliation (Kabat-Zinn, 2003; U.S. Religious Landscape Survey, 2013). Forth, other than discomfort and boredom MBIs involve little risk to patients. In the last forty years MBIs have been tested within a variety of clinical settings and patients, and only a few side effects have ever been documented (Praisman, 2008). Lastly, MBIs can be delivered in as little as 6-weeks (Carmody et al., 2009) and have long-lasting robust effects. Some participants of MBIs have reported sustained intervention effects up to three years post-invention without boosters (Grossman et al., 2007; Hofmann et al., 2010).

To summarize, MBIs could be beneficial for persons with SCD and chronic pain because (1) they have been used in a variety of other acute and chronic pain populations, (2) may help reduce symptoms associated with other comorbid chronic conditions, (3) can be delivered remotely, (4) don't conflict with religious beliefs, (5) are low risk, and (6) have long lasting effects.

### ***1.3 Conclusion***

Persons with SCD experience an array of biological, behavioral, and social complications. In addition to VOC and acute pain, persons with SCD experience chronic pain with far more frequency than what was previously believed. Finally, behavioral and social complications add to the complexity of disease and pain management. There are no standardized pharmacological treatment regimens for chronic pain in SCD, and there is a

lack of evidence-based non-pharmacological approaches to treat pain and pain catastrophizing for persons with SCD and chronic pain. Additional research is needed that explores the efficacy of non-pharmacological interventions for persons with SCD and chronic pain. A promising category of non-pharmacological interventions for managing pain in SCD are MBIs.

### **1.3.1 Purpose Statement and Aims**

The purpose of this dissertation is to (1) review non-pharmacological interventions for persons with SCD and chronic pain, (2) identify social and behavioral needs among a sample of adults during an ED visit for a VOC and explore the relationship between unmet social-behavioral needs to healthcare use, and (3) determine the feasibility and acceptability of a telephonic MBI designed for persons with SCD and chronic pain.

#### **1.3.1.1 Chapter 1**

##### *Aim 1*

Introduce the problem and significance.

#### **1.3.1.2 Chapter 2**

##### *Aim 1*

Analyze and synthesize the literature on non-pharmacological interventions for persons with SCD and chronic pain by conducting a systematic review of the literature.

### **1.3.1.3 Chapter 3**

Using a sample of 95 patients with SCD that received care at one of two hospitals in North Carolina for a VOC across 30 months:

#### *Aim 1*

Describe the frequency of acute care encounters (ED visits and day hospital visits) and hospital admissions;

#### *Aim 2*

Estimate the prevalence of behavioral (depression, anxiety, illicit drug use) and social (unemployment, unstable home situation) factors;

#### *Aim 3*

Determine the behavioral and social factors associated with increased acute care utilization and hospital admissions;

### **1.3.1.4 Chapter 4**

#### *Aim 1*

Evaluate the feasibility and acceptability of the telephonic MBI designed to reduce pain catastrophizing symptoms for adults with SCD and chronic pain.

#### *Aim 2*

Determine efficacy of the MBI relative to the control condition on pain catastrophizing as well as pain interference and severity, depression, health-related quality of life (mental and physical health), and mindfulness.

### **1.3.1.5 Chapter 5**

#### *Aim 1*

Summarize and discuss the significance of non-pharmacological approaches for persons with SCD, the relationship between unmet behavioral and social needs with healthcare utilization, and the potential use of a MBI for persons with SCD and chronic pain.

## **2. Chapter 2: A Review of Non-pharmacological Approaches for Pain**

### ***2.1 Introduction to Problem***

Sickle cell disease (SCD) is a life threatening condition that affects more than 7 million people world-wide (NHLBI, 2014). In the United States one out of every 375 African Americans is affected by sickle cell disease (SCD; Edwards et al., 2005), making SCD the most common genetic hematological disorder in the United States. Persons with SCD can suffer from many medical complications that may include, but are not limited to chronic anemia, stroke, acute chest syndrome, pulmonary embolus, renal failure, retinopathy, and many other serious complications (John, 2010; Claster & Vichinsky, 2003). By far the most common complication experienced by persons living with SCD, at some point in their life, is pain.

Persons with SCD experience both acute and chronic pain (Taylor et al., 2010). Acute pain is often caused by vaso-occlusive crises (VOCs), which are commonly described as unpredictable and excruciating. In addition to VOC pain, it is now understood that many patients with SCD also experience chronic pain. The Pain in Sickle Cell Epidemiological Study (PiSCES), a landmark longitudinal study that investigated sickle cell pain in 232 patients age 16 and over with SCD, found that chronic pain is much more common than VOCs or acute pain. In this longitudinal diary study of persons with SCD, patients reported chronic pain at home 38% of the time of the 31,000 days surveyed (Smith et al., 2008).

Among persons living with SCD, chronic pain (defined by the American Psychological Association as “pain that lasts longer than six months and affects how a person lives their daily life”) is associated with decreased social functioning, food consumption, physical activity, mobility, and negative emotions (McClish et al., 2005; Pells et al., 2005; Smith et al., 2005; Sadat-Ali, 1993). Typical negative emotions that may be experienced include recurrent feelings of fear, uselessness, and helplessness (Gil et al., 1992). In addition to these various psychosocial effects of chronic pain, persons with SCD and chronic pain have increased frequency and duration of pain (Gil et al., 1993), and overall worsening of physical health compared to persons without chronic pain (Booker et al., 2006).

Opioids have been the primary therapy used to treat both acute VOC and chronic pain in SCD. Concern of long term use of opioid therapy in recent years has led to the need to promote other non-pharmacologic therapies to treat chronic pain. Chronic opioid therapy only address the sensory/physical dimension of pain for persons with SCD, and does not address other dimensions of life effected by chronic pain including affective, behavioral, cognitive, cultural, or social dimensions. For these reasons, it is important that non-pharmacological therapies are investigated and used as complementary to pharmacological therapies to address and treat both acute and chronic pain for individuals living with SCD.

A range of non-pharmacologic therapies are used by individuals living with SCD for a variety of reasons. In a study that explored the use and perceived benefits of non-

pharmacological therapies by persons with SCD, 91.6% ( $n = 208$ ) patients reported using at least one type of alternative therapy for pain management, and 23% ( $n = 48$ ) reported benefits related to pain control by one of these approaches (Thompson & Eriator, 2014). This high usage of non-pharmacological therapies by persons with SCD has been replicated in other studies and ranges from 50% (Majumdar et al., 2013; Sibinga et al., 2006) to 70% (Yoon & Black, 2006). Some of the most common non-pharmacological therapies used by persons with SCD include cognitive behavioral therapy, biofeedback, prayer, relaxation techniques, acupuncture, hypnosis, herbal therapies, and megavitamins (Majumdar et al., 2013; Dampier et al., 2004).

Four evidence-based literature reviews of non-pharmacological therapies used by persons with SCD have been published (Hildenbrand et al., 2014; Edwards & Edwards, 2010; Chen, Cole, & Kato, 2004). These reviews categorize therapies primarily as either physical or psychosocial, or into one of the many psychological models (operant, peripheral physiological, cognitive and coping, behavioral, etc). In general, these reviews conclude that non-pharmacological therapies are effective in managing psychological and social complications of SCD, such as decreasing feelings of anxiety and depression, enhancing coping skills, and improving quality of life.

While helpful, these reviews focused on psychosocial factors such as anxiety or depression as primarily outcomes, not pain. None of these reviews directly addressed the effects of non-pharmacological therapies on pain itself (acute or chronic).

Several Cochrane reviews on SCD and non-pharmacological interventions (Anie & Green, 2002 & 2012) have also been published, but they too do not focus on pain as a primary outcome, only include psychological therapies, and do not discuss other non-pharmacological alternatives such as prayer, community support groups, exercise, and other approaches that are commonly used by persons with SCD to treat pain (Majumdar et al., 2013). In addition, a common limitation of all these reviews was their strict inclusion criteria (e.g., only randomized controlled trials, intervention delivered by certified clinicians, and quantitative evaluations only); that likely contributed to many relevant studies being excluded from these reviews.

Lastly, in 2014 the National Heart Lung and Blood Institute (NHLBI) published an expert panel report of evidence-based guidelines for the care of people with SCD (<http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/>). The recommendations conclude that there is a general lack of research in the area of non-pharmacological management of pain for persons with SCD, and that further randomized controlled trials (RCT's) are needed to determine the roles of alternative and supplemental therapies for the management of pain (NHLBI, 2014).

Therefore, a formal literature was conducted to describe and synthesize the use of non-pharmacological therapies for pain (of any type and origin) in persons SCD. A total of 28 articles are presented for review.

## **2.2 Methods**

A literature search was conducted using the following search engines:

PsychINFO, PsychARTICLES, PubMed, CINAHL, and EMBASE. Databases were searched using the following terms: *sickle cell*, *pain*, and *non-pharmacological therapies*.

In PubMed, *sickle cell* was searched using:

"Anemia, Sickle Cell"[Mesh] OR "sickle cell"[tiab]  
and *pain* in PubMed was searched with:

"Pain Management"[Mesh] OR "Pain"[Mesh] OR "pain"[tiab] OR  
"painful"[tiab] OR "pains"[tiab].

Search terms for *non-pharmacological therapies* in PubMed included:

nonpharmacological[tiab] OR "Complementary Therapies"[MeSH] OR  
complementary[tiab] OR alternative[tiab] OR "psychology"[Subheading] OR  
"Physical Therapy Modalities"[Mesh] OR physical therapy [tiab] OR  
"Diet"[Mesh] OR diet[tiab] OR dietary[tiab] OR "Nutrition Therapy"[Mesh] OR  
nutrition[tiab] OR "Psychotherapy"[Mesh] OR psychotherapy[tiab] OR behavior  
therapy [tiab]OR cognitive-behavioral[tiab] OR cognitive-behavioural[tiab] OR  
pain-behavior[tiab] OR psychological therapy[tiab] OR counseling[tiab] OR  
"Drugs, Chinese Herbal"[Mesh] OR herbs[tiab] OR herbal[tiab] OR "Mental  
Health Services"[Mesh] OR mental health[tiab] OR "Medicine,  
Traditional"[Mesh] OR "traditional medicine"[tiab] OR "Plant  
Preparations"[Mesh] OR "Plant Preparations"[tiab] OR "plant preparation"[tiab]  
OR "Exercise"[Mesh] OR exercise[tiab] OR exercises[tiab] OR exercising[tiab]  
OR "Minerals"[Mesh] OR minerals[tiab] OR mineral[tiab] OR "vitamins"[MeSH]  
OR vitamins[tiab] OR vitamin[tiab] OR acupuncture[tiab] OR "mind body"[tiab]  
OR holistic[tiab] OR biofeedback[tiab] OR massage[tiab] OR music therapy[tiab]  
OR mindful\*[tiab].

### **2.2.1 Study Inclusion and Exclusion Criteria**

Studies published in peer-reviewed journals that evaluated a non-pharmacological therapy for pain in persons with SCD were included in this review. Article eligibility included studies that tested a non-pharmacological intervention designed to affect change

in the intensity, duration, or frequency of pain (for either children or adults with a diagnosis of SCD), and written or translated into English. Dissertations were also included for review. Reference lists and bibliographies of eligible peer-reviewed articles were also searched for relevant material. Studies were excluded from review if they were not an intervention study, or artificially induced pain in their subjects (e.g., laboratory pain produced by temperature or pressure device).

### **2.2.2 Intervention Classification**

Similar to previous reviews on non-pharmacological therapies (Sansom-Daly et al., 2012; Plante, Lobato, & Engel, 2001) therapies were divided into three categories: peer-support group therapies, educational/psychoeducational therapies, and skill-based therapies. Each category is distinguished by their primary goal and intended outcome (Plante, Lobato, & Engel, 2001): (1) Peer-support group therapies are defined as those that aim to improve adaptation to illness through contact and support with peers, (2) educational/psych educational therapies are defined as those that aim to enhance adaptation to illness through information regarding the disease process and management, and lastly (3) skill-based therapies are defined as those that include or require explicit practical training, or the presence of a trained practitioner, to enhance illness adaptation (Sansom-Daly et al., 2012). Skill-based therapies were divided into dyadic (involved the presence of a parent or family member) and physical (involved physical manipulation of the body; e.g acupuncture, massage). In addition interventions were classified by target (acute pain versus chronic pain) and duration (single-session versus multi-session).

### **2.2.3 Methodological Quality**

The quality of each study was assessed using established criteria used in two literature reviews of non-pharmacological therapies (Sansom-Daly et al., 2012; Jackson, Cheater, & Reid, 2008). This methodological assessment approach was selected because it allows for scoring of qualitative, quantitative, and mixed methods research, and provides a structured approach to the review of study quality. Each paper was assessed using the following 18 criteria: (1) presence of theory or theoretical model, (2) clear aims/objectives, (3) clear description of setting, (4) clear description of sample, (5) appropriate sampling procedure, (6) intervention related homework or practice exercises, (7) intervention involvement with parent or family members, (8) face to face delivery of intervention, (9) peer to peer interaction in the intervention, (10) clear description of data collection, (11) clear description of how data were analyzed, (12) clear description of recruitment data and (13) attrition data, (14) found a statistically significant outcome, (15) measures tested for validity and reliability, (16) reporting all findings, (17) evidence of consumer involvement in intervention construction, and (18) stated strengths and limitations. For criteria satisfied a 1 was assigned if present, and 0 if not present or unclear. Articles therefore could have scored between 0 (no criteria met) to 18 (all criteria met).

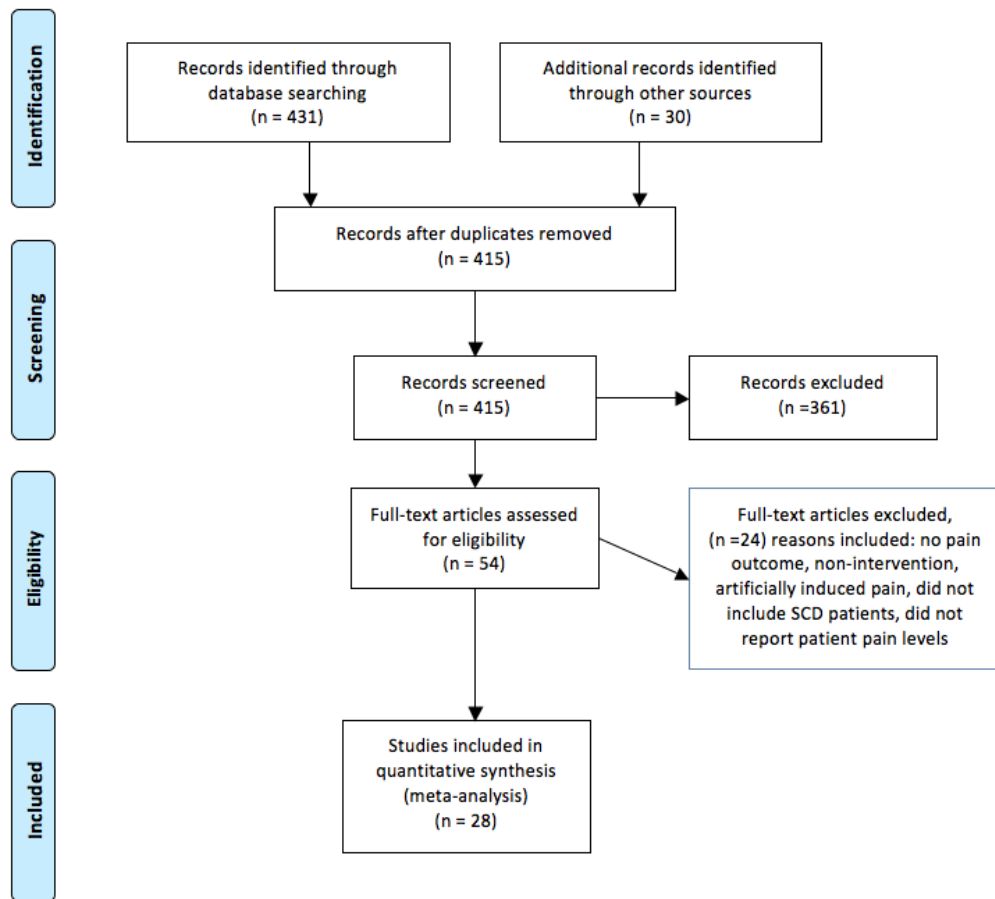
### **2.2.4 Effect Sizes**

To understand the magnitude of difference between intervention and control groups in pain outcomes, effect sizes were used. Effect sizes were calculated as the

difference in means between the intervention and control groups divided by pooled standard deviation of the two groups, with .20 considered as a small effect, .50 as a medium effect, and .80 considered a large effect.

### ***2.3 Results***

The search strategy yielded a total of 431 publications. Figure 1 presents the results of the structured literature review. Based on inclusion and exclusion criteria, removal of duplicates, screening of record titles, abstracts, and keywords, 54 articles received full text review, and 28 articles were retained and reported in Table 1 based on inclusion and exclusion criteria.



**Figure 1 - PRISMA Diagram**

### 2.3.1 Overview

Table 1 includes 28 articles that reported pain as one of the primary outcomes. Study samples were adults (n=12), children <18 years (n=4), children with their parents (n=6), and both adults and children (n=6). Sample sizes ranged from 1 to 227, with trials occurring in the United States (n=26) Netherlands (n=1) and Turkey (n=1).

The majority of therapies tested were either skill-based therapies or peer support group therapies. Skill-based therapies (cognitive behavioral therapy, biofeedback, hypnosis, massage, acceptance and commitment therapy, aquatic rehabilitation) were the most tested 23/28, of which six included parents or family, and eight involved physical manipulation of the body. Trained professionals were used to delivery the interventions in 14/28, while in the other 14 studies it was not clear if trained professionals were used. Of the 14 studies that used trained professionals, psychologists ( $n = 6$ ) were the most frequently used to delivery the therapy, followed by licensed massage therapists ( $n = 2$ ), and then nurses, physicians, and social workers ( $n = 6$ ).

Twelve studies yielded significant improvements in pain, three studies reported no positive effect or differences between experimental and control conditions on pain, and one study reported a negative or detrimental intervention effect. The study that reported a negative effect was a RCT of cognitive behavioral therapy (CBT) for adults with SCD that found pairing CBT with hydroxyurea increased the number of reported pain episodes (Lemanek, Ranalli, & Lukens, 2009).

Effect sizes were reported in 5 studies, and calculated for 4 studies (Table 1). In many cases it was not possible to perform effect size calculations due to missing data (e.g., failed to report  $\mu$ ,  $SD$ ,  $N$  related to pain outcome), or because effect size calculations were not possible based on the type of study design (e.g., cross sectional survey, case report). Effect sizes were low to medium in size, ranging from .12 (Braniecki, 2003) to

.58 (Cozzi, Tryon, & Sedlacek, 1987), with an average ( $\mu$ ) effect size of .332 across the nine studies.

**Table 1 - Summary of Reviewed Articles**

First Author/ Year	Design/Control Group	N/Population	Intervention/ Delivered by	Pain measures	Significance (Pain)	Pain Outcomes (note: $\bar{x}(s) = \text{mean}(SD)$ )	Study Quality (Scored 0-18; 0= worst and 18= best)	Effect Size
<b>Skill-based (physical)</b>								
Lemanek, 2009	RCT / massage vs attention control	34, Children (parent dyad)	Massage (with parents) / massage therapist (licensed)	Pediatric pain scale (Baker & Wong, 1987)	$P < .05$	Despite <i>P</i> value being reported, no mean/SD for pain scale reported in paper	14	N/A
Bodhise, 2004	One group pre-post test / no control	4, Children + adults	Massage / massage therapist	0-10 Numerical Pain Scale (NPS)	$p < .001$	Pre therapy NPS [9.6(.80)] Post therapy NPS [2.8(.75)]	10	N/A
Co, 1979	Crossover Design / accupuncture vs sham accupuncture control	10, Adults	Acupuncture / acupuncturist	Non-standardized verbal tool (Q1 - Do you have pain in your [name painful site]?) (Q2 - If yes, then is the pain the same, better or worse than it was the last time I saw you?)	$p > .05$	Nonsignificant difference between verbal report of pain reduction between sham and TX; both sham and actual acupuncture resulted in verbally reported patient pain reduction in 93% of all pain crises	6	N/A
Lu, 2013	Pre-post study design / no control	47, Adults	Acupuncture / acupuncturists (licensed)	0-10 Numerical Pain Scale (NPS)	$P < .001$	Pre to post therapy mean difference of 2.1 on the NPS (individual pre and post means/SD's not reported)	14	N/A
Myers, 1999	RCT/ massage relaxation training	16, Adults	Massage / massage therapist (licensed)	McGill pain questionnaire and Visual Analog Scale	$P < .001$	Pre therapy pain intensity 4.98(2.29) and unpleasantness 5.63(1.73); Post therapy 3.93(1.73) and 3.25(1.38)	13	.53

Thomas, 2013	RCT / healing touch vs. relaxation training	17, Adults	Healing touch / nurse	0-10 Numerical Pain Scale (NPS)	P > .05	Non significant differences; Pre-intervention NPS 6.83(1.85) to 4.55 (2.54) for healing touch, and 7.83 (1.59) to 7.17 (1.33) for relaxation control	13	.18
Tinti, 2010	case report / no control	1, Adults	Aquatic Rehabilitation / not clear	SF-36, McGill pain questionnaire, Wisconsin pain survey	p < .05	Pre to post therapy SF-36 = 50 to 93, McGill = 33 to 30, Wisconsin 10 to 7 (no standard deviations reported due to single person trial)	12	N/A
<b>Skill-based (dyad)</b>								
Barakat, 2011	RCT / CBT vs attention control	41, Children (parent dyad)	CBT (group) / psychologist	Pain Diary (Gil, 1994)	p = .86	Nonsignificant decrease % pain days from 24.94(29.64) to 16.71(23.03)	15	.35
Braniecki, 2003	RCT / CBT vs waitlist	16, Children (parent dyad)	CBT (group) / not clear	Pediatric Pain Questionnaire (Varni, Thompson 1987) Pain diary (Shapiro, 1990)	p < .001	Significant decreases parent pain score (p < .001) over course of study 18.39(3.64) to 9.61(4.70); Nonsignificant patient decrease in pain score 16.63(1.91) to 12.85(3.97) on PPQ and differences between tx and waitlist groups;	16	.12
Masuda, 2011	Case report / no control	1, Children (parent dyad)	Acceptance and Commitment Therapy / not clear	Pediatric pain scale (Varni, Thompson 1987)	no significance reported	Nonsignificant decrease in average pain (PPQ) pre to post intervention 15(SD=NR) to 10(SD=NR)	13	N/A
McElligott, 2006	RCT / writing vs. control	36, Children (parent dyad)	Writing / not clear	Pediatric Symptom Checklist for Youth (Jellinek & Murphy, 1990)	P > .01	No significant differences in pain,	15	.38

Powers, 2002	One group pre-post test / no control	3, Children (parent dyad)	CBT (group) / psychologist, hematologist, education specialist	Pain Diary (Gil, 1994) Daily Home Diary (Dinges et al., 1997; 10-point Likert Scale)	p > .05	No significant difference; did not report mean or SD;	15	N/A
Lemanek, 2009	RCT / massage vs attention control	34, Children (parent dyad)	Massage (with parents) / massage therapist (licensed)	Pediatric pain scale (Baker & Wong, 1987)	P < .05	Despite P value being reported, no mean/SD for pain scale reported in paper	14	N/A
<b>Skill-based (other)</b>								
Ağargün, 2001	Case report / no control	1, Children	Hypnosis / not clear	Pain measurement tool unclear and not described in case report	not reported	Begin with numerical score 6/7 item scale, reduce to unknown amount	2	N/A
Anie, 2002	One group pre-post test / no control	35, Adults	CBT / psychologist	Pain Interview (Anie et al., 2002; records patients' reports of frequency, intensity and duration of painful episodes and health care utilization within a 12-month period)	p > .05	Duration pain episodes (hrs) mean pre-therapy 114.7(112.4) to 90.0(56.7) post therapy; the number of pain episodes (over 12 months) pre-therapy 4.3(5.3) to 2.7(0.6) post therapy	14	.39
Cozzi, 1987	One group pre-post test / no control	8, Children + Adults	Biofeedback / not clear	Non-standardized 5-point pain intensity scale (1 = mild pain, 5 = pain requires hospitalization)	p < .05	Statistically significant decline pain intensity 1.92(NR) to 0.5 (NR) on 5-pnt scale, and statistically significant decreased number of self-treated pain crises 2.21(NR) to .44(NR) from weeks 1-4 to 9-12; standard deviations not reported	12	.58

Cummins, 2003	RCT / CBT vs hydroxyurea	36, Adults	CBT / not clear	Pain Interview (Anie et al., 2002; records patients' reports of frequency, intensity and duration of painful episodes and health care utilization within a 12-month period	p<.05	CBT compared to Hydroxyurea group had significantly more painful episodes 4.3(3.4) compared to 1.4(2.1), but shorter hospitalizations 2.4(2.7) to 7.2(5.5)	9	.19
Dignes, 1997	One group pre-post test / vs treatment as usual	37, Children + adults	CBT+ Hypnosis / not clear	Daily Pain Diary (Shapiro et al., 1990)	P < .05	Statistically significant decrease in % SCD pain days (20.41 to 10.65, p=.002) and days of other pain (18.92 to 5.83, p=.004)	14	N/A
Dobson, 2014	Quasi-experimental interrupted time series / no control	20, Children	Guided Imagery / certified child life specialist	Pediatric pain scale (Baker & Wong, 1987), daily diary (Dampier et al., 2002)	p < .05	Statistically significant decrease in pain frequency (5.6(3.3) to 2.5(4.1), p=.003); and pain intensity (2.4(1.2) to .7(1.2), p=.00)	14	N/A
Gil, 2001	RCT / CBT vs treatment as usual	46, Children	CBT / psychologist	Pain diary (Gil et al., 1994); Pain diary collects pain intensity (ranked 0-10), medication use (use of analgesics), health care contacts (ED visit), and activity reduction (yes/no)	P < .04	At follow-up, statistically significant more active approach to pain management 90(33.5) then control 57.44(30.9)	14	N/A
McClellan, 2009	Quasi-experimental / no control	19, Children	CBT (electronic device) / not clear	Daily Pain and Activity Diary (Combination of the Gil 1994 and Dinges 1997 pain diaries)	not reported	No pain outcome reported but intervention described as helpful by both parent 79(21.73) and child 81.44(21.58) on a 0-100 consumer satisfaction form	12	N/A
Thomas, 1999	RCT / CBT vs attention placebo group vs usual treatment	59, Adults	CBT (group) / psychologist	Pain Self-Efficacy Questionnaire (Nicholas, 1989), Short Form McGill Pain Questionnaire (Melzack, 1987), Beliefs About Pain Control Questionnaire (Skevington, 1990)	P < .05	Compared to attention control placebo and treatment as usual, CBT group had statistically significant decrease in pain intensity [pre therapy 14.3(10.45) to post therapy 8.3(8.89)]; treatment effect size .18; p < .008	15	.18

Thompson, 2014	cross sectional survey; retrospective/ no control	227, Adults	Prayer, Relaxation, Massage, Exercise, Spiritual healing, Herbal medicine, Yoga / (N/A)	Implemented a non-standardized 3 page survey created specifically for the study (did report chronbach alpha)	no significance testing for pain outcomes	91.6% respondents used CAM last 6 months, 23% reporting benefits of Prayer, Relaxation, Massage, and other CAM therapies	10	N/A
Zelter, 1979	case report / no control	2, Adults	Hypnosis / not clear	pain related hospital contacts over 4 and 8 months	no significance testing	No significance testing - patient reported improvement in frequency and intensity of pain crises with self-hypnosis techniques; reduction in hospital utilization from pre- to post-hypnosis training reported (no statistical testing)	4	N/A
<b>Peer-support Group</b>								
Butler, 1993	Cohort study / no control	24, Adults	Social support group / physician, psychologist, and social worker	not clear - appears to be collected by self-report and from patient interviews in group sessions	not reported	Patients self-reported improvements in recovery time from VOC's	5	N/A
Fox, 1999	case report / no control	NR, Children + Adults	Social support group / not clear	not clear - appears to be collected by self-report and from patient interviews	not reported	Only describe decreases in pain through relaxation training and biofeedback, no measures reported	3	N/A
Martin, 2005	RCT / social support group vs treatment as usual	40, Children + Adults	Social support group / not clear	Medical Outcome Survey (Stewart et al., 1988) [outcomes related to quality of life – mental and physical health, pain, etc.]	P < .05	Statistically significant increased in medical outcomes scores pre-intervention 65.32(25.82) to post intervention 71.71(20.17); but was not statistically significant when compared to control group (p=.167)	15	.27

Nash, 1993	Social support groups / no control	26, Adults	Social support group / professionals (unclear)	not clear (authors said that they "combined multiple measures used in self-help and sickle cell research" - no further description)	P < .05	Statistically significant negative correlation between length of group membership with disease symptoms scores (physical pain & psych), and total interference (no mean or SD provided)	14	N/A
Telfair, 1999	cross sectional survey; retrospective / no control	79, Children + Adults	Social support group / social workers and nurse coordinators	National SCD Adult Self Help Study's Sickle Cell Disease Problem Scale (Nash, 1991), 5-point likert pain scale (non-standardized, pain over last 30 days ranging from no pain to very severe pain)	p < .01	Subjects with high group satisfaction had significantly lower pain levels than those with low group satisfaction (f(3,75)=8.30, p<.01) [no mean or standard deviations reported]	14	N/A

### 2.3.2 Quality Assessment

The quality of the studies was fair. Quality assessment scores ranged from 2/18 to 16/18 (Braniecki, 2003; Ağargün, Öner, & Akbayram, 2001) with a mean of 11.61 and standard deviation of 4.18. Of the quality assessment factors, the majority of interventions involved face-to-face intervention delivery 26/28, and had clear aims/objectives 25/28 and descriptions of the study setting 27/28. Very few studies included parents or family members in the intervention 6/33, involved persons with SCD in the design of the intervention 3/33, or described a theoretical model 11/33.

Ten studies used a randomized controlled trial design, while two additional studies used control groups without randomization (pre-post design; Dinges et al., 1997), cross over design (Co et al., 1979)). Treatment as usual and attention control groups, which involved either interactions with clinicians or researchers, were used in eight studies (Lemanek, Ranalli, & Lukens, 2009; Barakat et al., 2010; Braniecki, 2003; McElligott, 2006; Dinges et al., 1997; Gil et al., 2001; Thomas, Dixon, & Milligan, 1999). While among the remaining studies, one tested their non-pharmacological therapy against hydroxyurea (Cummins & Anie, 2003), another against an active sham control (Co et al., 1979), and one against music (Thomas et al., 2013).

The measures used across the 28 studies to measure pain varied greatly. The most frequently used measurements for pain were the daily pain diary developed by Gil and colleagues (1994) ( $n = 5$ ), the McGill Pain Questionnaire ( $n = 3$ ), and either a 5-point or 10-point likert scale ( $n = 6$ ). The Coping Strategies Questionnaire developed by

Rosenstiel and Keefe (1983) ( $n = 9$ ) was the most frequently used instrument for pain-related outcomes. Validated pain measure with reported Cronbach's Alphas were found in 23 studies, while in the remaining 5 studies (Co et al., 1979; Ağargün, Öner, & Akbayram, 2001; Zeltzer, Dash, & Holland, 1979; Bulter & Beltran, 1993; Fox & Ingram, 1999) verbal reports of pain were captured thus Alphas were not applicable. Follow-up questionnaires were administered post-therapy in  $n = 9$  studies, and in 19 studies it was either not clear or not reported if follow-up questionnaires were administered post-therapy.

### **2.3.3 Intervention Target and Duration**

The intervention target (acute versus chronic) was clearly defined in eight articles. One article (McClellan et al., 2009) screened for persons with chronic (or recurrent) pain based on the American Psychological Definition, and seven articles differentiated chronic from acute pain (Lemanek, Ranalli, & Lukens, 2009; Lu et al., 2013, Cozzi, Tryon, & Sedlacek, 1987; Gil et al., 2001) or based on the number of vaso-occlusive crises (Powers et al., 2002, Cozzi, Tryon, & Sedlacek, 1987; Thomas, Dixon, & Milligan, 1999). The remaining 20 articles did not mention if the intervention targeted acute pain, chronic pain, vaso-occlusive pain, or a combination. For intervention duration, two studies involved single session interventions (Co et al., 1979; Ağargün, Öner, & Akbayram, 2001), three studies were not clear if one or more sessions were used (Bodhise et al., 2004; Bulter and Beltran, 1993; Fox & Ingram, 1999), and the remaining 23 studies involved multiple sessions.

### **2.3.4 Skills Training**

Nine of 23 the Skills Training Therapies reported significant reductions in pain. Cognitive Behavioral Therapy (CBT) was the most tested therapy (n=9). All of the CBT studies reported improvements in pain by participants, but only three demonstrated statistically significant reductions of pain. Several of these CBT therapies tested involved either a parent or family member in addition to the patient (Barakat et al., 2010; Braniecki, 2003; Powers et al., 2002), but of these group-CBT therapies only one showed significant decreases in pain (Braniecki, 2003). Five of the CBT studies reported longitudinal results that ranged from 3 months to 1 year, of which three studies showed lasting effects (6 months or longer) of the intervention on maintaining mild improvements in physical health (Barakat et al., 2010; Braniecki, 2003; Thomas, Dixon, & Milligan, 1999).

For the subset of skills training therapies that involved physical contact, massage (Lemanek, Ranalli, & Lukens, 2009; Bodhise et al., 2004; Myers et al., 1999), acupuncture (Co et al., 1979; Lu et al., 2013) healing touch (Thomas et al., 2013), and aquatic rehabilitation (Tinti et al., 2010) were tested. The three massage studies found statistically significant reduction in sensory pain scores, in addition to reduction in opioid use and number of hospitalizations (Bodhise et al., 2004). While the three acupuncture studies reported benefits to the therapy, but at non-statistically significant levels. Two of these three studies found that acupuncture decreased pain scores immediately following acupuncture; one reported it as not statistically significant (Lu et al., 2013), and the other

reported no significant difference in pain reduction when acupuncture was compared against a sham control (random use of acupuncture needles anywhere on the body) (Co et al., 1979). Lastly, a healing touch therapy found non-significant but trending decreases in physiological measurements of pain (Thomas et al., 2013), and an aquatic rehabilitation program found statistically significant reduction in pain along with increased respiratory muscle strength (Tinti et al., 2010).

Other skills training therapies tested, that were not CBT or physical therapies, included biofeedback (Cozzi, Tryon, & Sedlacek, 1987), hypnosis (Ağargün, Öner, & Akbayram, 2001; Dinges et al., 1997; Bulter & Beltran, 1993), and guided imagery (Dobson & Byrne, 2014). Of these therapies, only two (Cozzi, Tryon, & Sedlacek, 1987; Dobson & Byrne, 2014) found statistically significant improvements in pain or pain-related outcomes. The biofeedback study failed to find statistically significant improvements in pain, but was trending toward improvements in pain intensity, pain episodes, and amount of pain medication needed (Cozzi, Tryon, & Sedlacek, 1987). Hypnosis was found to significantly reduce the number of pain days and pain-related medication consumed when combined with CBT (Dinges et al., 1997), otherwise non-significant improvements in pain, medication usage, and pain-related hospitalizations were found in the two other studies (Ağargün, Öner, & Akbayram, 2001; Zeltzer, Dash, & Holland, 1979). Lastly, a study using guided imagery in children ( $n = 20$ ), four sessions across two months, found statistically significant reductions in pain episodes and pain intensity (Dobson & Byrne, 2014).

### **2.3.5 Peer Support**

Three of the five studies that involved peer-support group therapies reported significant improvements in pain (Martin, 2005; Nash & Kramer, 1993; Telfair and Gardner, 1999), while all five reported positive improvements for pain. The two studies that did not find statistically significant improvements in pain still reported patients felt that the therapy was clinically effective in improving pain (Bulter & Beltran, 1993; Fox & Ingram, 1999). Three studies included both children and adults in the support groups (Fox & Ingram, 1999; Martin, 2005; Telfair and Gardner, 1999), while two were exclusive to only adults (Bulter & Beltran, 1993; Nash & Kramer, 1993). Regarding pain reduction, three studies found that the degree of pain sensation and pain interference was buffered by social support groups (Martin, 2005; Nash & Kramer, 1993; Telfair and Gardner, 1999).

### **2.3.6 Educational**

Lastly, there were no studies that tested educational/psychoeducational therapies and examined pain reduction as the outcome. In our broad literature search there were nine studies that tested educational interventions for persons with SCD (Baskin, 2000; Collins et al., 1997; Duncan et al., 1992; Jackson, 1995; Kaslow & Brown, 1995; Kaslow et al., 2000; Koontz, 1998; Lloyd, 2008; Porter et al., 2014), but none include pain as an outcome and thus were excluded in this review.

## ***2.4 Discussion***

To the best of our knowledge, this is the first literature review to report findings on non-pharmacologic interventions for the treatment of pain in SCD. In this review, 28 non-pharmacological interventions for persons with SCD were examined. Of these studies, a wide variety of non-pharmacological interventions were tested. Some of these interventions were based on psychological principles (e.g., cognitive behavioral therapy), while others were based on physical (e.g., massage therapy, aquatic rehabilitation), social (e.g., dyadic and group therapies), or alternative foundations (e.g., prayer, acupuncture, acceptance-based therapy). In addition to a diversity of interventions, there also existed a range of methodological approaches, of which included quantitative, qualitative, and mixed methods.

### **2.4.1 Implications for Future Research**

The interventions that lead to improvements in this review are broadly categorized into two types: skill-based interventions (subdivided into physical, dyadic, and other) and peer-support groups. *Skill-based* interventions are defined as those that include or require explicit practical training or the presence of a trained practitioner to enhance illness adaptation, and *Peer-support Group* interventions are defined as those that aim to improve adaptation to illness through contact and support with peers (Sansom-Daly et al., 2012).

#### **2.4.2 Intervention Target and Duration**

Intervention target (acute pain versus chronic pain) should be clearly defined in future studies. Eight of the 28 studies differentiated acute versus chronic pain in either their sample or inclusion criteria. Future studies should use the 2014 National Heart Lung and Blood Institute (NHLBI) recommendations for SCD, which clearly describes various types of pain, such as acute pain, acute recurrent painful crises, neuropathic pain, or chronic pain, in addition to chronic pain of unclear etiology, chronic pain related to an objective cause, chronic neuropathic pain, or “breakthrough” pain. Additional specificity related to the type of pain targeted by the intervention may help improve clinical decision making and the pairing of the correct intervention to pain type, just as one would do for a pharmacological intervention (e.g., right patient, right drug, right dose, right time, right route).

The vast majority of studies (23 studies) involved multi-session interventions, compared to only two articles that reported using single session interventions of acupuncture (Co et al., 1979) and hypnosis (Ağargün, Öner, & Akbayram, 2001). Based on the present findings it cannot be determined if single session interventions are more or less effective than multi-session interventions for reducing acute or chronic pain. Because of the limited number of single-session intervention studies, we suggest that future studies explore the efficacy of single-session versus multi-session interventions for pain reduction. Interventions that can be delivered in a single-dose format may be especially useful for persons with SCD due to transportation difficulties (getting to and from clinical

appointments), frequent hospitalizations, and physical disabilities, all of which can make it difficult to have re-occurring (weekly, bi-weekly) appointments that require physical presence.

### **2.4.3 Skills-based Therapies**

Of the 23 skills-training interventions reviewed, approximately half reported significant reductions in pain. A variety of skills-training interventions were tested that included massage therapy, acupuncture, biofeedback, hypnosis, cognitive behavioral therapy, guided imagery, and aquatic rehabilitation. The intervention with the strongest supporting evidence in our review, as also in three other reviews (Edwards & Edwards, 2010; Chen, Cole, & Kato, 2004; Anie & Green, 2012), is cognitive behavioral therapy (CBT).

Compared to the other approaches reviewed, CBT has the most randomized controlled trial studies, and is the only non-pharmacological approach that is also supported by the NHLBI guidelines with a ‘strong degree of evidence’ (NHLBI, 2014; Chen, Cole, & Kato, 2004). Having established that CBT is an effective non-pharmacological intervention for persons with SCD, it is recommended that future researchers continue exploring other types of interventions listed that either (1) have not been rigorously tested with active control groups (e.g., massage, biofeedback, dyadic therapy), or (2) interventions that have shown promising results in other chronic pain populations but have not received extensive testing in SCD (e.g., mindfulness-based

interventions such as Mindfulness-based Stress Reduction and Acceptance and Commitment Therapy).

#### **2.4.4 Peer-support Group Therapies**

Only five peer-support studies were eligible in this review. In comparison to the 23 skill-based therapies (in which 10 were RCT design studies), only one peer-support group study implemented a RCT design, while the other four were either case-reports or single-cohort studies. And out of these five studies, the most recent was published one decade ago (Martin, 2005). But despite a limited number of studies, these five studies do provide preliminary evidence that peer-support group interventions can influence physical outcomes (e.g., pain) for persons with SCD. And as reflected in the findings of these studies, future studies should be aware that the success of improving physical symptoms, like pain, can be significantly influenced by group satisfaction and the length of group membership (Nash & Kramer, 1993; Telfair & Gardner, 1999).

Even though a low quantity of research was found in this review to support the use of peer-support groups in pain management for persons with SCD, more evidence does exist to support the use of peer-support groups, but only for disease specific education (e.g., genetic education; Kaslow et al., 2000; Porter et al., 2014). It is important that research in this area continues as many hospitals and other healthcare institutes continue to offer peer-support groups for patients with SCD and other chronic conditions.

## 2.4.5 Methodological Limitations and Recommendations

Even with a clear potential for the use of non-pharmacological therapies for pain management in SCD, there are several reoccurring methodological limitations amongst these studies that must be addressed in future research.

First, it is important that future intervention studies for persons with SCD clarify: (1) If the intervention targets acute pain or chronic pain, and (2) the etiology of the patients' pain. In the latest recommendations published by the National Heart, Lung, and Blood Institute, *Evidence-Based Management of Sickle Cell Disease* (1), chronic pain etiology for persons with SCD is differentiated into four categories: chronic pain of unclear etiology, chronic pain related to an objective cause, chronic neuropathic pain, and "breakthrough" pain. By clarifying whether an intervention targets acute or chronic pain, and the etiology of the pain targeted, future interventions may become more targeted and prescribed to patients based on their type of pain. For example, persons with chronic pain related to avascular necrosis of the hip may benefit more from a non-pharmacological approach like Mindfulness-based Stress Reduction (MBSR), versus someone in a sickle cell pain crises (e.g., different pain etiology) may receive no benefit at all from a approach like MBSR. But to achieve this it is essential that more clarity and description of the pain type and etiology is provided in future studies.

Second, the impact of race and socioeconomic status for persons with SCD should also be accounted for in future studies. Historically, non-pharmacological interventions (e.g., psychological interventions like cognitive behavioral therapy) were constructed and

tested within samples that were mostly Caucasian, not African American. Of the interventions reviewed, there is little to no discussion on how racial or cultural differences may have impacted participation in these interventions. Because the majority of persons with SCD in the United States are African American (Yusuf et al., 2010), there is a need to acknowledge and test interventions for racial, cultural, and socio-economic sensitivity. But despite an apparent absence of racial or cultural sensitivity in the testing of these interventions, many participants found them to be helpful.

Future studies should also be wary of frequent hospitalizations and transportation issues faced by many persons with SCD that might influence their availability to be physically present for these interventions. Persons with SCD can experience frequent hospitalizations and emergency department visits. Between 1999 and 2007 SCD accounted approximately 200,000 emergency department visits per year (Yusuf et al., 2010), and in 2010 persons with SCD had the highest hospital readmission rate of any disease (Elixhauser & Steiner, 2010). By offering virtual or mobile equivalents of the intervention, persons with SCD that are frequently (or currently) hospitalized, or experience frequent scheduling difficulties because of their disease, will still be able to participate despite not being physically present. Additionally, virtually delivered interventions may prove very useful for those that are unable to drive because of their condition, or regularly afford transportation because of low socioeconomic status.

Lastly, the potential usefulness of these interventions for decreasing pain described in this review should be interpreted with caution, as methodological issues such

as small sample sizes, lack of active control groups, and combining adult and pediatric results, make it difficult to generalize reported findings. The 12 studies that reported mixed-aged samples (n=6 children with parents, n=6 children and adults) did not report pediatric versus adult differences. Future studies could compare and contrast pediatric versus adult samples for differences in intervention efficacy and pain type (acute versus chronic), since it is possible that a proven therapy for children with acute pain (e.g., visualization or group-CBT) may not be as effective for adults with chronic pain, or vice versa.

The broad inclusion criteria used for many of these studies (e.g., only asking for persons with a diagnosis of sickle cell) also makes it difficult to generalize findings across the various types of pain often experienced by persons with SCD (acute, chronic, crises, etc.), and levels of disease severity [e.g., SS, SB<sup>0</sup> (sickle cell anemia) versus SC and SB<sup>+</sup>]. Furthermore, the use and frequency of pain medications, both prescribed and non-prescribed should be included as important study outcomes. Because many persons with SCD manage their pain outside of the hospital on their own, it is important to account for interactions and potential additive effects of the patient's own pain management practices.

#### **2.4.6 Limitations of this Review**

The scoring guidelines used to critique study quality in this review is unfortunately biased towards randomized controlled trial (RCT) designs. Even though it can still be used for non-RCT studies, it is not equally weighted for criteria related to

qualitative or mixed research designs. Additionally, this criteria was originally created for non-pharmacological interventions in pediatric populations, which is why some items such as ‘the presence of a parent or family member’ were include in the assessment. Despite these drawbacks, this scoring method was explicitly developed for assessing the quality of non-pharmacological pain research, and to the authors knowledge, there are no other scoring criteria available in this domain of research that have been validated and cited in other reviews.

Second, the original intent of the review was to synthesize and describe the literature on non-pharmacological therapies specifically for chronic pain, not general pain (as we did), in persons with SCD. After a thorough review of the non-pharmacological therapy literature for persons with SCD and chronic pain, we found only one article (McClellan et al., 2009) that reported screening persons with chronic (or recurrent) pain based on the American Psychological Definition of chronic pain. There were four additional articles that either defined or differentiated chronic (or recurrent) pain from acute pain or pain associated with vaso occlusive crises (Lemanek, Ranalli, & Lukens, 2009; Lu et al., 2013; Cozzi, Tryon, & Sedlacek, 1987; Gil, Anthony, & Carson, 2001), and three studies that screened patients on the number of vaso occlusive crises either within the last month (Powers et al., 2002) or year (Cozzi, Tryon, & Sedlacek, 1987; Thomas, Dixon, & Milligan, 1999). Because of the limited amount of literature found in this initial search, the scope of this review was broadened to include any type of pain

experienced by persons with SCD. As the non-pharmacological literature grows in SCD it will be important that this question is re-asked and answered.

Third, only physical pain outcomes were included and summarized in this review. The majority of studies reviewed contained pain-related outcomes (e.g., depression and anxiety, sleep, quality of life) and other important indicators of clinical value for researchers, but were excluded because these findings have been summarized elsewhere (Edwards & Edwards, 2010; Anie & Green, 2012). We do note that many of these secondary outcomes, such as anxiety and depression, were found to be positively impacted by the non-pharmacological interventions in our review and generally perceived as helpful by participants.

Lastly, the calculated effect sizes demonstrate a small effect of non-pharmacological interventions on pain in persons with SCD ( $\mu = .332$ ), but these results should be interpreted with caution. Only nine studies were used to calculate the  $\mu$  intervention effect size on pain, and these nine studies had small sample sizes (range  $n = 8-51$ ) which raises concerns related to statistical power and ability to detect statistically significant differences between intervention and control groups. In addition, a variety of non-pharmacological interventions were tested (e.g., CBT, massage, biofeedback) that differed in length, and pain type (e.g., acute, chronic, nociceptive, neuropathic, vaso-occlusive crisis) in calculating the  $\mu$  intervention effect size.

## ***2.5 Conclusion***

Approximately half of the studies reviewed demonstrated success in alleviating pain, suggesting that: (1) patients are able to use non-pharmacological interventions with some degree of success, and (2) it is possible to study these alternative interventions. Other reviews on non-pharm interventions in SCD that have focused on pain related outcomes (e.g., anxiety, depression, quality of life) have come to similar conclusions: that non-pharmacological interventions can lead to health improvements (Edwards & Edwards, 2010; Chen, Cole, & Kato, 2004). But despite the success and potential application of these interventions, there are many questions yet to be answered regarding the efficacy and generalizability of these interventions for persons with SCD.

### **3. Chapter 3: Behavioral and Social Factors Associated with Healthcare Utilization in Sickle Cell Disease**

#### ***3.2 Introduction and Background***

Sickle Cell Disease (SCD) is a life threatening condition that affects more than 7 million people worldwide (NHLBI, 2014). In the United States one out of every 375 African Americans is affected by sickle cell disease (SCD; Edwards et al., 2005), making SCD the most common genetic hematological disorder in the United States. SCD primarily affects African Americans and those of Caribbean descent, but is still found in Caucasians from southern Europe and the Mediterranean, and in people from the Middle East and India (El-Hazmi, Al-Hazmi, & Warsy, 2011). In the 1990s the average lifespan for men and women with SCD was between 42 and 48 years (Platt et al., 1994), but because of penicillin prophylaxis and increased hydroxyurea prescription and use, the average lifespan has increased to 58-66 years (Elmariah et al., 2014).

Pain is the hallmark symptom of SCD. In addition to experiencing debilitating chronic and neuropathic pain (NHLBI, 2014), persons with SCD experience acute painful episodes known as a vaso-occlusive crises (VOCs). A VOC is caused by an accumulation of sickled red blood cells in the vasculature, resulting in damage (acute pain) to surrounding tissue areas (Frenette, 2002). In general VOC's are described as sudden onset, unpredictable, debilitating and excruciating. Some persons with SCD are aware of specific factors that can provoke a VOC, although they may not be able to fully control these factors.

Due to disease complexity and difficulty treating VOCs, it is not uncommon for persons with SCD to have frequent ED visits, hospital admissions, and hospital readmissions. Between 1997 and 2007 there were approximately 1.6 million visits (197,000 p/year) by persons with SCD (Yusuf, Atrash, Grosse, Parker, Grant, 2010). Of the hospital admissions and ED visits, VOC's account for approximately 76.9% of hospital admissions and 64.2% of ED visits (Brousseau et al., 2010). In 2010 the highest 30-day readmission rate of any acute and chronic condition was Sickle Cell (31.9% of all readmissions), accounting for approximately 87,326 hospital admissions and 27,837 readmissions (Elixhauser & Steiner, 2013). Over the course of 50-year life expectancy the projected costs for healthcare services with SCD is estimated at \$8,747,908.00 per person (Ballas, 2009). It is important to recognize that even though SCD is associated with a high number of high ED visits, approximately 54% of ED visits come from a small subset of SCD patients (between 16% and 35%) who average 7.4 visits per year (Brousseau et al., 2010; Alsiku et al., 2009; Epstein et al., 2006). Persons with SCD that visit the ED or have more than four hospital admissions in one year are known commonly referred to as high utilizers (Carroll, Haywood, Fagan, & Lanzkron, 2009).

To help reduce unnecessary ED visits and hospital admissions for persons with SCD, some hospitals have adopted a 'day hospital' treatment model to better manage uncomplicated VOCs (Benjamin, Swinson, & Nagel, 2000). In a day hospital, persons with SCD are treated for uncomplicated VOCs (e.g., a VOC not associated with a medical emergency such as acute chest syndrome) within an outpatient center, typically

by a nurse practitioner, and then sent home the same day to continue with home oral pain medicines (Raphael et al., 2008). A day hospital visit, compared to an ED visit is less expensive (Adewoye et al., 2007), and compared to a hospital admission, is associated with faster pain relief and shorter length of stay (Raphael et al., 2008).

A limited number of patient factors have been associated with utilization of healthcare services by persons with SCD. Medical factors include history of transfusion and prior hospital admission for pain (Sobota et al., 2012), underuse of hydroxyurea (Okam, Shaykevich, Ebert, et al., 2014), withdrawal syndrome related to low opioid dosing at hospital discharge (Ballas & Lusardi, 2005), low hematocrit level, more transfusions, diagnosis of asthma, or requiring supplemental oxygen to maintain normal saturation at time of ED discharge (Aisiku et al., 2009; Frei-Jones, Field, & DeBaun, 2009).

In comparison to medical factors, far less is known about what, if any behavioral or social factors are associated with healthcare utilization. The prevalence of depression and anxiety is known to be high among individuals with SCD, ranging from 2% to 57% (Levenson et al., 2008; Jonassaint et al., 2016), and is exacerbated by SCDs chronicity and unpredictable pain crises (Molock & Belgrave, 1994). The presence of depression and anxiety predict more daily pain, higher opioid use, along with poorer mental and physical health in persons with SCD (Levenson, et al. 2008). A recent systematic review of depression in SCD adults found an association between depression and increased healthcare utilization (Jonassaint et al., 2016), but did not report what provoked the need

for each visit (e.g., vaso-occlusive crisis versus acute chest syndrome versus stroke), or the type of visit (e.g., hospital admission versus day hospital versus emergency department).

To manage challenges related to depression and anxiety, persons with SCD report using negative coping skills, such as avoidance to manage feelings of depression and anxiety (Citero et al., 2007; Booker et al., 2006). But the use of negative coping strategies such as avoidance (e.g., suppressing undesirable cognitions and emotions) may increase the number of ED visits or hospital admissions, and perpetuate misuse of prescribed opioids (Garland, Brown, Howard, 2016).

While from a social perspective, SCD contributes to social exclusion, financial stress, and disease-related stigmatization (Scott & Scott, 1999; Elander et al., 2004). Many patients report having unmet social needs related to transportation, maintaining stable social relationships and employment, and ability to pay medical costs (Bulter & Beltran, 1993; Pettignano, Caley, & Bliss, 2011). For low-income children with SCD, low parental socio-economic status has been associated with significantly higher healthcare utilization by the child (Raphael et al., 2009). It is not known if the association between low socio-economic status and healthcare utilization continues into adulthood for persons with SCD. For adults with SCD seeking treatment for a VOC, relatively little is known about how social factors (e.g., unstable home situation and unemployment) and behavioral factors (e.g., anxiety, depression, and illicit drug use) may influence

healthcare utilization (McCrae and Lumley, 1998; Sogutlu et al., 2011; Glassbery, Wang, Cohen, et al., 2012).

The overarching goal of this research was to better understand the prevalence of behavioral (anxiety, depression, and illicit drug use) and social (unstable home situation, unemployment) factors and their association with healthcare utilization in persons with SCD seeking care a VOC. Using a sample of 95 patients with SCD that received care at one of two hospitals in North Carolina for a VOC across 30 months, we addressed the following specific aims:

- (a) Describe the frequency of acute care encounters (ED visits and day hospital visits) and hospital admissions;
- (b) Estimate the prevalence of behavioral (depression, anxiety, illicit drug use) and social (unemployment, unstable home situation) factors;
- (c) Determine the behavioral and social factors associated with increased acute care utilization and hospital admissions;

### ***3.3 Methods***

#### **3.3.1 Design**

This project was conducted as part of a larger project aimed to improve the management of VOC care for persons with SCD. In this paper, we report results from a prospective correlational study to identify behavioral and social factors associated with increased healthcare utilization ( $N = 95$ ). The Institutional Review Board at both study sites approved the project, and patients provided informed written consent to be contacted

within two weeks of an acute care encounter, for an interview to collect behavioral and social information. A waiver of consent was provided to review the number of acute care encounters and hospital admissions for the entire study period.

### **3.3.2 Setting**

The study was conducted at two hospitals in the Southeast. Both hospitals were academic medical centers with emergency medicine residency programs. Site-1 had approximately 130 nurses, 27 total emergency medicine residents, and 21 emergency medicine (EM) faculty. At Site-2 there were approximately 146 nurses, 43 EM residents, and 37 EM faculty. Additionally, both hospitals had day hospitals at the time of the study that were open Monday-Friday, 8A-4P.

### **3.3.3 Procedures**

#### **3.3.3.1 Sample and Recruitment**

All adult patients ( $\geq 21$  years of age) with an acute care encounter for the treatment of a VOC were eligible for inclusion. Research assistants reviewed all acute care encounters and patients admitted to the hospital through the ED on a daily basis. Patients were recruited and consented in-person, either during a hospital admission related to a VOC, or at the end of an ED visit between April 2012 and March 2014. Patients consented to participate in an interview within two weeks of a future acute care encounter, should one occur. Patients consented to be contacted after any acute care encounter or hospital admission for the entire study period. Patients were not allowed to contribute more than a total of five interviews over the study period.

### **3.3.3.2 Patient Interviews**

Interviews were conducted from April 2012 to March 2014. Research staff monitored hospital admission and ED logs (ED visits) daily to identify patients who had had an ED visit and previously consented to participate in a follow-up interview. Research staff identified 10 patients per quarter per site to interview using the following stratification system 1) admission status (yes/no), 2) number of acute care encounters in the past 3 months ( $\leq 2$ , 3-4,  $\geq 5$ ), and 3) whether or not the patient had previously participated in an interview specific to this study. These criteria were used to ensure a representative sample of unique patients (many patients had more than one acute care encounter during the study period, all attempts to interview unique patients were made), and a representative sample of admissions vs. discharges, as well as patients with high and low utilization. Using the stratification process, every three months 10 patients (per site) were selected to participate in a follow up interview and contacted within 14 days of a acute care encounter, and received either an in-person (if hospitalized) or telephone interview. Interviews were conducted as close to the acute care encounter index visit as possible and no greater than two weeks after the ED visit. Upon the completion of an interview, patients received a \$10 gift card for their time.

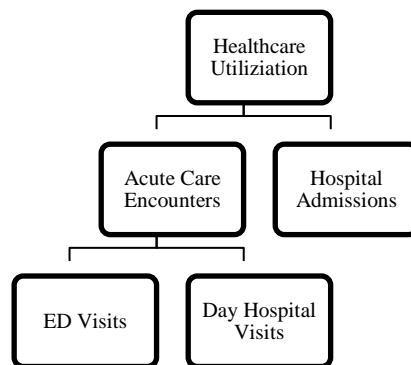
The focus of the interview was to evaluate behavioral and social factors. The behavioral factors included “are you generally anxious”, “are you generally depressed”, and “do you use illicit drugs or abuse alcohol”. Social factors were “do you live in an unstable home situation,” and “are you currently employed”. Potential selections for the

behavioral factors were yes, no, and unsure, and for the social factors selections were yes, no, and intermittent. These were selected questions from Decision 7 (Referrals) of Emergency Department-Sickle Cell Assessment of Needs and Strengths (ED-SCANS). The ED-SCANS is an evidence-based, decision support and quality improvement framework developed to guide care for SCD patients in the ED. The ED-SCANS tool was developed by conducting a series of focus groups across the United States with emergency physicians and nurses, and patients, and by literature review and fieldwork (Tanabe et al., 2013). The ED-SCANS has been found to have excellent inter-rater, face and utility validity by ED nurses and physicians, with construct validity for behavioral (anxiety and depression) questions, and rated as a clear, relevant, and easy to use (88-100%) as a decision support tool (Tanabe et al., 2013). The two items taken from the ED-SCANS for depression and anxiety have high convergent validity with the Spielberger Trait Anxiety Scale (STAI) and the Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) (Tanabe et al., 2013). These single item screening items were developed to allow for use in a busy ED. The two social items (employment and stable home) have not been cross-validated with other measurement tools.

### **3.3.3.3 Health Care Utilization – Medical Record Reviews**

Healthcare utilization data was captured from October 2011 to March 2014. Figure 2 depicts healthcare utilization categorization, defined as (1) frequency of acute care encounters and (2) frequency of hospital admissions. Acute care encounters was defined as the number of ED visits and day hospital visits. Because of the similarities in

treatment of VOCs provided by the ED and day hospital, ED and day hospital visits were combined and operationalized into the category *acute care encounters*. Acute care encounter is therefore a combined count of all ED visits and day hospital visits per patient. To obtain the frequency of healthcare utilization, a report of all ICD-9 codes associated with a VOC (282.6, 282.60-64, 282.68-69) between October 2011 and March 2014 was generated for each of the  $n = 95$  patients in the sample. Each acute care encounter (ED visit or day hospital visit) and hospital admission were counted as unique visits. If a patient had an ED visit and hospital admission in the same day it was counted as two visits, and if they had an ED visit, day hospital visit, and hospital admission in the same day it was counted as three visits.



**Figure 2 - Healthcare Utilization Categorization**

### **3.3.4 Data Analysis**

Non-directional statistical tests were conducted with the level of significance set at 0.05 unless otherwise specified. Statistical Analysis Software (SAS 9.3) was used to analyze the data.

Descriptive statistics were used to summarize the demographic characteristics of individual patients with SCD in the sample at the first interview conducted for the total sample (N=95) and per site (Site-1: N=56; Site-2: N=39). The number of interviews conducted per patient and site was also determined. Due to severe skewness, a non-parametric Wilcoxon Two-Samples Test was used to test for between-site differences in age. Chi-square tests were performed to test for between-site differences in gender, race, and proportion of patients with two or more interviews. The following methods were used to address Aims *a-c*.

(a) The following was determined for the total sample and for each site: (1) total number of acute care encounters (ED and day hospital visits) and hospital admissions, and (2) the number of acute care encounters and hospital admissions per patient with SCD. Wilcoxon Two-Sample Tests were used to test for site-differences in the healthcare utilization per patient.

(b) Number and percent of patients with SCD who reported behavioral (depression, anxiety, and illicit drug use) and social (unstable home situation, unemployment) factors were assessed. Chi-square/Fisher's Exact Tests were used to test for site-differences in behavioral and social factors. For patients with one or more interviews, if a patient responded 'unsure' to depression, anxiety, or drug use during any interview they were categorized and coded as 'no' for the study period, and if a patient responded 'intermittent' to unstable home or employment, they were categorized and coded as 'yes' for the study period. Lastly, if a patient participated in more than one

interview and had both 'yes' and 'no' responses for the same question but in different interviews (e.g., reports both yes and no for depression), the 'yes' response was retained.

(c) Analysis of covariance procedures using the rank scores (Ranked ANCOVA, controlling for site) were conducted to identify behavioral (depression, anxiety, illicit drug use) and social (unemployment, unstable home situation) factors that are associated with the number of acute care encounters, hospital admissions, and/or total utilization. Due to the severe skewness of the utilization data for each healthcare category, the number of acute care encounters and/or hospital admissions per person was rank ordered. In the event of tied ranks, the mean of the tied ranks was used. Site was included as a covariate to control for site differences with regard to patient demographic/clinical characteristics. Each ANCOVA was performed using the Type III sum of squares results from a General Linear Model. Each model was designed to test for the effect of each behavioral/social factor on the mean of the rank scores for the utilization category, after controlling for site. Separate analyses were conducted for each factor and each utilization category measure. Any behavioral or social factor significant at the 0.05 level was retained for inclusion in a subsequent multi-factor ANCOVA. Least square means of the rank scores, adjusted for site effects, were derived from the models. For all analyses, higher rank scores represented a greater number of acute care encounters and/or hospital admissions per person.

### 3.4 Results

*Sample Characteristics.* Table 2 provides a summary of the patient demographic characteristics reported at the initial interview completed. Among the 95 individuals with SCD in the sample, the median age was 27.5 years. Most of the patients were African American (97%), with three individuals indicating that they were multi-racial or other. Patients at Site-1 were significantly older than the patients at Site-2 ( $z=2.44$ ,  $p=.0143$ ), while Site-2 had a significantly greater proportion of females (chi-square=12.18,  $df=1$ ,  $p=0.0005$ ). The two sites did not differ with regard to racial/ethnic composition ( $p>.05$ ).

**Table 2 - Patient Demographic Characteristics**

Characteristic	Total (N=95)	Site-1 (N=56)	Site-2 (N=39)	P-value
Age, in years				
Median	27.5	29.0	25.0	0.0143
25 <sup>th</sup> , 75 <sup>th</sup> percentile	23, 36	25, 38	22, 31	
Minimum, maximum	18, 58	18, 58	18, 53	
Female, <i>n</i> (%)	45 (48%)	18 (33%)	27 (69%)	0.0005
African American, <i>n</i> (%)	92 (97%)	54 (96%)	38 (98%)	0.7824
Hispanic/Latino, <i>n</i> (%)	4 (4%)	3 (6%)	1 (2%)	0.6324
Fisher's Exact Test performed for Hispanic /Latino ethnicity due expected cell count less than 5.				

Table 3 provides the total number of patient interviews completed for the total sample and at each site. The 95 patients participated in a total of 156 interviews over the 30-month period. The number of interviews completed per patient ranged from 1 to 5. The majority of the patients (60%) were interviewed one time, with Site-1 having a greater proportion of patients with one interview relative to Site-2 (Site-1=70%; Site-2=46%; chi-square = 5.29,  $df=1$ ,  $p=0.0215$ ).

**Table 3 - Number of Patient Interviews**

<b>Interviews</b>	<b>Total (N=95)</b>	<b>Site-1 (N=56)</b>	<b>Site-2 (N=39)</b>
Number of interviews	156	78	78
Number of interviews per patient			
One interview, <i>n (%)</i>	57 (60%)	39 (70%)	18 (46%)
Two interviews, <i>n (%)</i>	23 (24%)	13 (23%)	10 (26%)
Three interviews, <i>n (%)</i>	8 (8%)	3 (5%)	5 (13%)
Four interviews, <i>n (%)</i>	6 (6%)	1 (2%)	5 (13%)
Five interviews, <i>n (%)</i>	1 (%)	0 (0%)	1 (3%)

(a) *Frequency of Healthcare Utilization.* Table 4 presents the healthcare utilization for the total sample and per site. There were 2829 acute care encounters (ED and day hospital) and 1101 hospital admissions, resulting in total utilization of 3930. Site-1 had a greater number of acute care encounters than Site-2.

**Table 4 - Total Number of Acute Care Encounters and Hospital Admissions for the 95 Patients**

<b>Category</b>	<b>Total</b>	<b>Site-1</b>	<b>Site-2</b>
<b>Acute Care Encounters</b>	<b>2829</b>	<b>1692</b>	<b>1137</b>
ED visits	1990	962	1028
Day hospital visits	839	730	109
<b>Hospital Admissions</b>	<b>1101</b>	<b>556</b>	<b>545</b>
Acute Care Encounters & Hospital Admissions	3930	2248	1682

Table 5 provides a summary of healthcare utilization per patient (patient-level data). The median number of acute care encounters and hospital admissions per person over the 30-month period was 27 (range=1 to 201). The median number of acute care

encounters was 19 (range=1 to 181), while the median number of hospitalizations was 7 (range=0 to 50). The median number of ED visits per patient was lower at Site-1 than Site-2 (9.5 vs 15;  $z=1.93$ ,  $p=0.0530$ ), but the median number of day hospital visits was significantly higher at Site-1 relative to Site-2 (4 vs 1;  $z=-3.36$ ,  $p=0.0011$ ).

Among the 95 patients, 25% had utilization at or exceeding the following during the 30-month period: (a) 35 acute care visits; (b) 29 ED visits; (c) 9 day hospital visits; (d) 19 hospitalizations; (e) 55 acute care encounters and/or hospital admissions. This “high user” subgroup included patients with fewer ED visits and more day hospital visits at Site-1 when compared to Site-2 (ED Visits: Site-1=24.5 vs Site-2=45; Day hospital visits; Site-1= 11.5 vs Site-2 = 3), while the number of acute care encounters and hospital admissions was very similar at each site. The utilization counts for the upper 25% of the sample are denoted by the 75<sup>th</sup> percentile and maximum values for healthcare utilization per person in Table 5.

**Table 5 - Number of Acute Care Visits and Hospitalizations per Patient**

Category	Statistic	Total (N=95)	Site-1 (N=56)	Site-2 (N=39)	P-value
Acute Care Visits					
	Median	19	19	17	0.6883
	25 <sup>th</sup> , 75 <sup>th</sup>	8, 35	5.5, 33	10, 45	
	Min, Max	1, 181	1, 181	1, 152	
ED visits					
	Median	13	9.5	15	0.0530
	25 <sup>th</sup> , 75 <sup>th</sup>	5, 29	4, 24.5	8, 45	
	Min, Max	1, 151	1, 72	1, 151	
Day hospital					

visits					
	Median	2	4	1	0.0011
	25 <sup>th</sup> , 75 <sup>th</sup>	0, 9	0.5, 11.5	0, 3	
	Min, Max	0, 109	0, 109	0, 24	
Hospitalizations					
	Median	7	7	10	0.1750
	25 <sup>th</sup> , 75 <sup>th</sup>	3, 19	3, 12.5	3, 20	
	Min, Max	0, 50	0, 40	0, 50	
Acute care & hospitalization					
	Median	27	27	27	0.4009
	25 <sup>th</sup> , 75 <sup>th</sup>	11, 55	9, 51	15, 55	
	Min, Max	1, 201	1, 201	1, 176	
ED = Emergency Department; 25 <sup>th</sup> , 75 <sup>th</sup> = percentile, Min, Max = Minimum, Maximum.					

(b) *Behavioral and Social Factors.* Table 6 reports the behavioral and social factors for the total sample and per site. Approximately one-third of the sample reported feeling depressed (29%) and having anxiety (34%). Illicit drug use was reported by 6% of the patients. Site-1 had a significantly lower rate of depression reported than Site-2 (20% vs 44%; chi-square=6.34, df=1, p=0.0118). Among the 95 patients, 17% reported living in an unstable home situation and 81% indicated that they were not currently working. The sites did not differ on these two social characteristics (p>.05).

**Table 6 - Behavioral and Social Factors**

	<b>Total (N=95)</b>	<b>Site-1 (N=56)</b>	<b>Site-2 (N=39)</b>	<b>P-value</b>
<b>Behavioral, n (%)</b>				
Depression	28 (29%)	11 (20%)	17 (44%)	0.0118
Anxiety	32 (34%)	20 (36%)	12 (31%)	0.6159
Illicit drug use	6 (6%)	4 (7%)	2 (5%)	1.0000
<b>Social, n (%)</b>				
Unstable home	16 (17%)	12 (21%)	4 (10%)	0.1756

Unemployment	76 (81%)	42 (76%)	34 (87%)	0.1892
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(c) *Behavioral and Social Characteristics Associated with Frequency of Acute Care Encounters and Hospital Admissions.* The ANCOVA results, which examined the effects of the behavioral and social factors on the mean rank for the number of acute care encounters, hospital admissions, and total utilization per person after controlling for site, are summarized in Tables 7-9. Illicit drug use was omitted from the analytic models due to the small number of patients (n=6) who reported this behavior.

Table 7 details the acute care encounter (ED and day hospital visits) results. Although not statistically significant, the results indicated that patients with an unstable home situation tended to have a higher number of acute care visits (Mean rank=58.3, SD= 28.2) than those with a stable home (Mean rank=46.3, SD=21.2, p=0.1176). Furthermore, patients who were unemployed had a significantly higher mean number of acute care visits (Mean rank=51.5, SD=27.4) than those who were employed (Mean rank=35.0, SD=24.4, P=0.0231). In terms of descriptive statistics for illicit drug use, those patients reporting drug use had a higher mean number of acute care visits (Mean rank = 64.1, SD=23.3, n= 6) compared to those without drug use (Mean rank=46.9, SD=27.6, n=89, no test).

**Table 7 - ANCOVA: Acute Care Encounters per Person**

Model	Model Terms	F	df	P-value
1	Depression	0.50	1, 92	0.4816
	Site	0.04	1, 92	0.8374

2	Anxiety	0.13	1, 92	0.7208
	Site	0.15	1, 92	0.7031
3	Unstable home	2.49	1, 92	0.1176
	Site	0.40	1, 92	0.5277
4	<b>Employment</b>	5.34	1, 91	<b>0.0231</b>
	Site	0.00	1, 91	0.9991
Rank ordered utilization data analyzed. Site included as a covariate.				

Table 8 summarizes the hospital admissions results. Patients with an unstable home situation tended to have a higher mean number of hospital admissions (Mean rank=59.3, SD= 34.2) than those with a stable home (Mean rank=46.7, SD=25.8, p=0.0962). Patients who were unemployed had a significantly higher mean number of hospital admissions (Mean rank=51.7, SD=27.3) than those who were employed (Mean rank=35.4, SD=25.1, P=0.0241). Finally, patients reporting illicit drug use had a higher mean number of hospital admissions (Mean rank = 63.5, SD=23.0, n= 6) compared to those without drug use (Mean rank=47.0, SD=27.6, n=89, no test). A multi-factor model was not because employment was the only characteristic associated with acute care encounters at the 0.05 level.

**Table 8 - ANCOVA: Hospitalizations per Person**

Model	Model Terms	F	df	P-value
1	Depression	0.15	1, 92	0.7010
	Site	1.47	1, 92	0.2277
2	Anxiety	0.01	1, 92	0.9255
	Site	1.86	1, 92	0.1765
3	Unstable home	2.83	1, 92	0.0962
	Site	2.60	1, 92	0.1105
4	<b>Employment</b>	5.26	1, 91	<b>0.0241</b>

	Site	1.09	1, 91	0.2981
Rank ordered utilization data analyzed. Site included as a covariate.				

Table 9 summarizes the total utilization (acute care encounters and hospital admissions) results. Patients who were unemployed had a significantly higher mean number of total utilization (Mean rank=51.7, SD=27.3) than those who were employed (Mean rank=34.7, SD=24.7, P=0.0192). Patients with an unstable home situation tended to have a higher mean number of total utilizations (Mean rank=57.7, SD= 29.0) than those with a stable home (Mean rank=46.7, SD=27.2, p=0.1479). Patients reporting illicit drug use had a higher mean number of total utilization (Mean rank = 64.6, SD=22.1, n= 6) compared to those without drug use (Mean rank=46.9, SD=27.6, n=89, no test).

The pattern of findings for total utilization was similar to those for the acute care encounters and hospital admissions when analyzed separately. Employment was the only characteristic associated with the different measures of utilization at the 0.05 level and site was not a statistically significant covariate in the any of the models (p>0.05).

**Table 9 - ANCOVA: Total Utilization per Person**

Model	Model Terms	F	df	P-value
1	Depression	0.34	1, 92	0.5586
	Site	0.43	1, 92	0.5113
2	Anxiety	0.12	1, 92	0.7252
	Site	0.67	1, 92	0.4147
3	Unstable home	2.13	1, 92	0.1479
	Site	1.11	1, 92	0.2952
4	<b>Employment</b>	5.69	1, 91	<b>0.0192</b>
	Site	0.21	1, 91	0.6482
Rank ordered utilization data analyzed. Site included as a covariate.				

### ***3.5 Discussion***

To the best of our knowledge, this is the first attempt to understand the relationship between behavioral and social factors associated with acute care encounters and hospital admissions for persons with SCD seeking treatment for a VOC in a prospective manner. From a sample of 95 adult patients with SCD who received care for a VOC at one of two southeastern hospitals in the US, we reported healthcare utilization, behavioral and social factors, and associations between behavioral and social factors with healthcare utilization. We found (1) high utilization of healthcare services, a median of 27 acute care encounters and hospital admissions per patient, (2) high prevalence of depression (29%), anxiety (34%), and unemployment (81%), and (3) unemployment being the only factor associated with greater frequency of acute care encounters and hospital admissions per person.

#### **3.5.1 Healthcare Utilization**

The number of acute care encounters and hospital admissions per patient was relatively high, a finding that is shared by other studies that have assessed healthcare utilization by persons with SCD (Sogutlu et al., 2011; Brousseau et al., 2010). Similar to prior studies, there was large variation in the number of acute care encounters and hospital admissions among individual patients. This finding is shared by many SCD studies, and is related to a small percentage of patients that account for the majority of healthcare utilization (Aisiku et al., 2009).

Prior studies have not reported, or decimated between the different types of healthcare services that are frequently utilized by persons with SCD seeking treatment for a VOC. By distinguishing between ED visits, day hospital visits, and hospital admissions, an interesting trend became visible. ED utilization per patient was significantly lower at Site-1 then Site-2, and day hospital utilization per patient was significantly higher at Site-1 compared to Site-2 per patient. As previously stated, the function of a day hospital is to provide pain management for uncomplicated VOCs in order to avoid unnecessary ED visits or hospital admissions. Future studies should investigate the hypothesis that there is an inverse relationship between day hospital visits and ED visits/hospital admissions for uncomplicated VOCs at treatment centers that offer a day hospital service. The associated differences in costs for the treatment of VOC by using day hospital services should also be explored.

### **3.5.2 Behavioral and Social Characteristics**

The prevalence of depression and anxiety was common at both study sites. These findings corroborate other studies that have reported similarly high levels of depression and anxiety among adults with SCD (Sogutlu et al., 2011; Levenson et al., 2008; Laurence, George, & Woods, 2006). Interestingly, there was a significant difference in prevalence of depression between Site-1 and Site-2. Both Site-1 and Site-2 employ dedicated SCD social workers, but only Site-1 has a dedicated SCD psychologist. It is possible that the presence of a dedicated SCD psychologist significantly impacted the reported prevalence of depression by patients at Site-1.

Additionally, it was unknown whether or not patients would be willing to share information regarding illicit drug use, but we found patients were willing to share this sensitive information. Their willingness to share is extremely important because of the misconception that many persons with SCD are drug abusers. In one study 53% of ED physicians thought more than 20% of SCD patients are addicted to drugs (Shapiro et al., 1997), while in another study 63% of nurses believed that the majority of SCD patients are addicted to drugs (Pack-Mabien et al., 2001). Our finding supports that only a very small percentage of persons with SCD report using illicit drugs (5-7%). Other studies have found similar findings regarding drug abuse and addiction behavior in SCD. In 2003 Elander and colleagues reported only 4% of persons with SCD showed DSM-IV substance dependence symptoms that were non-pain related (Elander et al., 2003), and that the majority of drug seeking behavior observed and labeled as addiction by providers is actually pseudoaddiction but misinterpreted as addiction (Elander et al., 2004). Individuals with pseudoaddiction display behaviors of addiction in the context of trying to obtain analgesics for pain when healthcare providers are reluctant to treat pain. Our result should be interpreted with caution though as it is a measure of self-report and not an objective measure such as a drug screen.

Our sample demonstrated a high social burden with 81% reporting being unemployed and 17% reported living in an unstable home. Disease severity often negatively impacts ones' ability to maintain employment. Because the majority of persons with SCD live below the federal poverty line (Pettignano, Caley, & Bliss, 2011),

and have trouble maintaining employment and thus income (Pereira et al., 2013), many persons with SCD experience a wide range of unmet social needs that are related to a lack of financial resources.

The reported prevalence of depression, anxiety, and unemployment, is opportunity for social worker intervention or psychological referral. A social worker is an important, yet often underutilized hospital resource that can help with many of these unmet social needs. Both sites have a dedicated SCD social worker and ED social worker, but at the time of this study there was no systematic process at either site to alert a social worker to the presence of a SCD patient during an acute care encounter. After completion of the project, Site 1 instituted a standard process to identify, screen and refer all patients with SCD for social services during an ED visit. It is important that future work determine how social worker resources can be made more readily available to persons with SCD seeking treatment for a VOC.

### **3.5.3 Associations between Behavioral and Social Factors with Healthcare Utilization**

One of the surprising results of this study was the lack of any finding between the behavioral factors (anxiety, depression, illicit drug use) and healthcare utilization. A recent meta-analysis of depression in SCD children and adults found an association between depression and healthcare utilization (Jonassaint et al., 2016), but this study did not report on the type of visit (e.g., ED versus DH versus hospital admission) or visit purpose (e.g., treatment for acute chest syndrome versus vaso-occlusive crisis). While other studies that have examined similar behavioral constructs in SCD have found mixed

results. For example, somatic burden has been associated with higher utilization for only VOC related treatment (Tsao et al., 2014), but has also been associated with higher utilization for only non-VOC treatment (Sogutlu et al., 2011). Pain catastrophizing has shown no relationship to either VOC or non-VOC related utilization (Citero et al., 2007). Studies that have used non-SCD chronic pain patients, with smaller sample sizes and less statistical power, have shown that behavioral factors (e.g., pain catastrophizing) are strongly associated with increased utilization and duration of hospital visits, pain intensity and behavior, and analgesic consumption (Sullivan, Bishop, & Pivik, 1995; Keefe et al., 2000; Jacobsen & Butler, 1996; Bedard et al., 1997; Gil et al., 1992; Gil et al., 1993; Keefe et al., 1989).

So somewhat surprisingly, our lack of any finding between the behavioral factors (depression and anxiety) and healthcare utilization for persons with SCD is partially supported. The PiSCES study that found high somatic burden with comorbid depression and anxiety was not associated with ED visits for persons with SCD for a VOC (Sogutlu et al., 2011). This suggests that behavioral factors such as depression and anxiety are unrelated to ED visits for VOC, but could be related to other types of non-VOC visits.

Unemployment was the only social or behavioral factor associated with higher utilization. This is an important finding because 81% of the sample reported being unemployed. It is possible that unemployment is a proxy measure of disease severity. To the best of our knowledge, no other studies have tested or reported on unmet social needs and healthcare utilization in SCD seeking treatment for VOC pain, but other non-SCD

studies have found significant associations between unmet social needs and healthcare utilization in other chronic illnesses (Nieuwenhuijsen, Stam, et al., 2008; Osher, Drake, 1996). A closely related study conducted in England did report that persons with SCD who live in socio-economically deprived areas are at higher risk for hospital readmission (54%) compared to those in areas of less socio-economic deprivation (28%), and mortality (Aljuburi et al., 2013). However, no descriptions were provided within this study on what specific social factors were included within the ‘deprivation’ variable other than it was based on the “lower super output area index of multiple deprivations franks for the whole of English”. In summary, future research should explore the effect of such high unemployment rates on patients centered outcomes and overall healthcare utilization.

### ***3.6 Limitations***

Our sample reflects patients treated in two large EDs affiliated with a comprehensive SCD center, each with dedicated social and behavioral health services. It is possible that patients that are not affiliated with a comprehensive center may have even higher social and behavioral health needs. We cannot make any conclusions on how this would change healthcare utilization. Per our protocol, only ICD-9 codes associated with VOC (282.6, 282.60-64, 282.68-69) were used to measure utilization. We do not know how many additional acute care encounters or hospital admissions occurred (e.g., uncomplicated VOCs not related or comorbid with acute chest syndrome, stroke, priapism, infection, etc.).

### ***3.7 Conclusion***

In summary there was a high number of acute care encounters and hospital admissions per person at both study sites. Our sample experienced a high burden of behavioral health needs and an extraordinarily high percent (81%) of unemployment. None of the social or behavioral factors, except for unemployment, were associated with increased frequency of acute care encounters or hospital admissions for persons with SCD seeking treatment for a VOC.

## **4. Chapter 4: A Telephonic Mindfulness-based Intervention for Persons with Sickle Cell Disease and Chronic Pain**

### ***4.1 Introduction***

Sickle Cell Disease (SCD) is a genetic hematological disorder that affects more than 7 million people globally (NHLBI, 2009). It is estimated that 50% of adults with SCD experience pain on most days, with 1/3 experiencing chronic pain daily (Smith et al., 2008). Persons with SCD also experience higher levels of pain catastrophizing (feelings of helplessness, pain rumination and magnification) than other chronic pain conditions, which is associated with increases in pain intensity, pain behavior, analgesic consumption, frequency and duration of hospital visits, and with reduced daily activities (Sullivan, Bishop, & Pivik, 1995; Keefe et al., 2000; Jacobsen & Butler, 1996; Bedard et al., 1997; Gil et al., 1992; Gil et al., 1993; Keefe et al., 1989). A promising category of non-pharmacological interventions for managing both physical and affective components of pain are Mindfulness-Based Interventions (MBIs) (Thompson et al., 2010; Cox et al., 2013).

There is strong evidence to support the use of MBIs for persons suffering from chronic pain. Mindfulness-based interventions teach patients that sensing pain, even if it is intense or chronic, does not need to be fought, ignored, suppressed, or inhibit them from living a meaningful life or accomplishing their goals (Vowles, McCracken, & Eccleston, 2008). This approach challenges patients to decrease pain-related cognitive and emotional reactivity that can increase distress and exacerbate pain (e.g., pain

catastrophizing), and to engage in active coping of the present moment (Kabat-Zinn, 1990). The mindfulness approach is thus very different than other types of non-pharmacological therapies like Cognitive behavioral therapy (CBT). In CBT a patient is taught to recognize and reframe negative thought patterns to change how they are feeling (e.g., *analyzing thoughts*; Burns et al., 2015). While in a MBI the patient is taught not to reframe negative thoughts but to notice and accept thoughts (e.g., *experiencing thoughts*) and then redirect their focus back on the present moment (Day et al., 2014). Mindfulness interventions can thus be viewed as more of a naturalistic observation or participant-observation (open monitoring) of thoughts versus a purposeful reframing of thoughts like in CBT. For both approaches multiple systematic and Cochrane reviews on their utility for pain and pain coping have been published, which largely support the use of both MBI and CBT approaches (Veehof et al., 2011, Hofmann et al., 2012).

While MBIs have shown positive effects, the generalizability of these results for persons with SCD is unknown. Some MBIs (e.g., Mindfulness-Based Stress Reduction [MBSR]) require eight weekly classes, homework assignments, and daily practice (30-45 minutes per day), which may be too much of a burden for persons with SCD and chronic pain. Second, non-adherence rates for routine clinical appointments for persons with SCD are reported as high as 46% (Robinson et al., 2006), so it is unknown if persons with SCD are able to adhere to a weekly MBI schedule. Third, persons with SCD are not typically prescribed non-pharmacological interventions. Many persons with SCD are prescribed hydroxyurea and chronic opioids to manage their disease, and have little exposure to

additional therapeutic interventions; with the most common alternative therapy used by persons with SCD being prayer (Clayton-Jones, D., & Haglund, 2015). Lastly, the majority of current MBIs have been developed and tested with non-minority (Caucasian) samples, so there is uncertainty as to whether a MBI would be seen as acceptable, feasible, or as effective in a predominately minority sample (e.g., African Americans with SCD). To our knowledge, no study has investigated the feasibility or acceptability of an abbreviated MBI, delivered telephonically for persons with SCD and chronic pain.

The overall goal of this pilot randomized controlled clinical trial (RCT) was to explore the feasibility and acceptability an abbreviated 6-session MBI that is targeted for persons with SCD and chronic pain, and to obtain preliminary data on the efficacy of this intervention relative to a wait-listed control condition on pain catastrophizing and other pain-related outcomes. The specific aims were to: (1) Evaluate the feasibility and acceptability of the telephonic MBI designed to reduce pain catastrophizing symptoms for adults with SCD and chronic pain; (2) Determine efficacy of the MBI relative to the control condition on pain catastrophizing as well as pain interference and severity, depression, health-related quality of life (mental and physical health), and mindfulness.

## ***4.2 Methods***

### **4.2.1 Overview**

This was a single-site, pilot RCT comparing MBI and a wait-listed control condition with assessments at four time points (baseline, week 1, week 3, and week 6) in adult patients with SCD and chronic pain. Individuals who provided written informed

consent were enrolled in the study. Enrolled and randomized patients were aware of their assignment to either a MBI or control condition, and were not blinded to the study aims. The MBI was conducted as a 10-person group teleconference call, led by a certified MBI instructor. A 2:1 treatment allocation was implemented in this initial pilot study so as to collect more data on the feasibility and acceptability of the MBI. Feasibility included measures of enrollment, randomization, attendance, intervention completion, along with assessment completion. Acceptability was assessed with semi-structured interviews conducted with randomly selected MBI participants. The primary efficacy outcome was pain catastrophizing total score. The study is registered with [clinicaltrials.gov](https://clinicaltrials.gov) (NCT02394587), received approval from the Institutional Review Board at Duke University, and informed written consent was obtained from all participants prior to participation.

#### **4.2.2 Setting and Sample**

Patients were recruited from an outpatient comprehensive SCD center in the Southeast. An interdisciplinary team of physicians, nurses, psychologists, and social workers run the center, providing care for approximately 600 SCD patients. The target sample for this pilot study was 60 patients with SCD and chronic pain, with 40 patients randomly assigned to MBI and 20 patients to the control condition. With a sample size of 60, the study did not have at least 80% power to detect a significant difference between the MBI and control conditions on the primary outcome of pain catastrophizing with a

level of significance set a 0.05 (two-tailed). However, the focus of this pilot study was to estimate treatment effect sizes rather than conduct statistical significance testing.

### **4.2.3 Eligibility Criteria**

Patients meeting the following criteria were eligible for inclusion: (a) self-reported diagnosis of SCD, age 18 and older, (b) self-identified as having chronic, non-cancer pain that persists on most day for more than 6 months that adversely affects their function or well being, (c) ability to speak and read English, (c) access to a landline or cell phone, and (d) access to a CD or mp3 player. Patients were excluded if they: (a) Previously participated in a MBI study (e.g., MBSR, mindfulness-based cognitive therapy or intervention), or (b) regular practitioners of mindfulness, including yoga.

### **4.2.4 Recruitment**

Participants were recruited from an outpatient comprehensive SCD center from April 2015 to November 2015. The center medical director approved and supervised in-person patient recruitment at the center, and remote recruitment by mail.

*In-person* recruitment occurred immediately before, or after a patients' clinical appointment. Prior to being approached by study personal, patients were pre-screened by their healthcare provider to assess their general capacity to participate (e.g., ability to provide consent), and current involvement in other research studies. Patients already enrolled in a cognitive or behavioral intervention study were not approached for recruitment due to the potential of carryover effects between interventions. A recruitment script was used to discuss the study with potential participants, verify the presence of

chronic pain per the study definition, and solicit participation. Individuals who meet all inclusion criteria, and verbally agreed to participate, then signed a consent form and received a study packet containing a copy of the consent form, headphones, a mindfulness-practice CD, and four copies of assessments. For participants who had an email address, identical digital versions of the questionnaires were provided through hyperlinks that were managed with REDCap electronic data capture tools (Harris et al., 2009).

*Recruitment letters* were mailed in waves of 50, to patients who had a scheduled appointment at the outpatient center within the next two weeks. This decision was made because there existed no rigorous method to determine which patients were suffering from chronic pain. The recruitment letter provided the study purpose, inclusion criteria (including definition of chronic pain), participant involvement, and contact information for the study PI. Based on previous research experience in the center, including poor response to recruitment letters, the recruitment letter used IRB-approved opt-out language to notify patients that the PI would contact them via phone to describe the study unless the patient informed the PI via phone or email that they do not want to be contacted. A period of 2 weeks was provided prior to initiating phone calls after the mailing was sent to allow potential subjects time to contact the PI. Three attempts to contact the patient were made before determining the patient was not interested in participating. The same recruitment script used for in-person recruitment was used to discuss the study with potential subjects by phone. Individuals who meet all inclusion

criteria, and verbally agreed to participate were then be mailed a consent form along with the study packet.

#### **4.2.5 Randomization Procedures**

Patients who provided informed written consent and met the participant selection criteria were enrolled and randomized using a 2:1 treatment allocation to either MBI or control condition. Because the MBI condition was group-based, randomization of participants was divided into four cohorts of 15 participants to reduce the amount of idle time between informed consent and intervention delivery. After the first cohort of 15 participants provided informed consent, they were randomly assigned to either the MBI ( $n=10$ ) or a control condition ( $n=5$ ). The random number function in Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) was used to randomize patients to either the MBI ( $n = 40$ ) or control condition ( $n = 20$ ) using a permuted block randomization scheme to achieve a 2:1 allocation. Within each block size of 15, ten patients were randomized to receive MBI and 5 were randomly assigned to the wait-listed control condition.

Within two weeks of randomization, participants either began the MBI, or their time in the control condition. Following randomization and initiation of the first cohort of 15 patients, the next cohort of 15 patients were recruited and randomized following the same protocol. This continued until 60 participants were randomized for a total of 4 cohorts.

#### **4.2.6 Retention Strategies and Compensation**

In an attempt to prevent participants from dropping out before the MBI started, a proactive retention strategy was used to retain participants that had been randomized, but not yet participated in the MBI. Participants received weekly contact via telephone and email, and were provided with information regarding how many more participants were needed before the intervention could begin. After beginning the MBI program, participants randomized to the MBI received either a telephone call, text message, or email (their choice) the morning of each mindfulness session, and again 1-hr before each session. In addition, all participants received weekly and bi-weekly contact by study personal to remind them of their study participation, upcoming due dates for assessments, and when compensation (checks) had been mailed to their home address.

Three monetary payments were provided to help increase retention and compensate participants for their time: (1) \$10.00 after baseline assessments were received and/or participation in MBI Session 1; (2) \$20.00 after receiving measurements at the end of week three and/or participation in MBI Session 3; and (3) \$30.00 at the conclusion of the study upon receiving the final measurements, and/or participation in MBI Session 6. All subjects in the in MBI and control group received payments upon return of each assessment according to this schedule. In addition to providing monetary compensation, the MBI program was provided at no cost to subjects, a value of over \$400.00.

#### **4.2.7 Mindfulness-based Intervention Condition (MBI)**

Participants randomized to the MBI condition received a telephonically delivered MBI program. The MBI adapted core elements from John Kabat-Zinn's original Mindfulness-based Stress Reduction (MBSR) program (Kabat-Zinn, 1985), and targeted common symptoms, emotions, and stressors related to chronic pain experienced by persons with SCD. We developed the telephonic MBI through an informal process that involved iterative feedback from patients, clinical experts in SCD and pain management, social workers, psychologists, and mindfulness clinicians. Through this process, relevant topics and skills were selected from the original MBSR program to adapt in each MBI session.

Based on the needs described, and keeping in line with adapting specific elements of MBSR, the original MBSR content was simplified and compressed into six, 60 minute telephonic group sessions that taught: (1) breath awareness (focus on breath and observing thoughts without fighting or following them; weeks 1-6); (2) body scan (promoting mindfulness of sensations in different parts of body; weeks 2-6); (3) walking meditation (walking as form of meditation; weeks 3-6); (4) loving kindness (projection of friendliness and kindness towards oneself and others; weeks 4-6); and (5) choiceness awareness (awareness of all sensations with equal interest; weeks 5-6). Each of these practices, which are all part of the original MBSR program, focus on cultivation and practice of mindfulness techniques. Breath awareness, body scan, loving-kindness, walking meditation, and choiceless awareness promote and foster 'open monitoring' and

intentional observation of thoughts, feelings, and bodily sensations (Kabat-Zinn, 1982). With guidance from the mindfulness instructor, participants are presented with various examples of how each exercise can be infused with everyday tasks (e.g., doing the dishes, brushing teeth). Currently there is much debate on the mechanisms and how each of these practices may elicit changes for pain-related outcomes (Day et al., 2014), but because the MBI contains components of exposure therapy the walking meditation and body scan exercises may contribute to decreased pain-related disability by reducing fear of movement and fear of pain (Crombez et al., 2012). At this time, researchers are actively engaged in trying to better understand the mechanisms of mindfulness and how mindful practices may specifically help those with pain (Creswell, 2016; Day et al., 2015; Zeidan et al., 2015, 2016).

Table 10 summarizes the intervention used in this study and compares it to typical MBSR programs. The first ten minutes of each session were used to review previous material, followed by approximately 20 minutes of instruction and overview of a new mindfulness exercise, 15 minutes of mindfulness practice, with the remaining time for questions. Because each session was conducted as a group teleconference call, the size of each MBI session was limited to a maximum of ten patients (plus the mindfulness instructor) to minimize caller interruptions and disruptions.

Our decision to reduce the number of minutes per each session, and remotely deliver the MBI, is supported by the MBI literature. Prior studies have found time commitment to be a common barrier to recruitment and MBI completion (Ho, 2012; Ngo

et al., 2011), and a non-significant correlation between the number of in-class hours and effect size of a MBI (Carmody & Baer, 2009). Therefore the number of minutes per session was reduced to sixty, a number we believe is more amenable to the subject's other obligations (e.g., work and family activities), and the number of weekly sessions from eight to six. Second, it is difficult for some persons with SCD to find transportation to and from the clinic; therefore an intervention that is easily assessable by telephone may increase the likelihood of recruitment, retention, and program completion. The literature supports the delivery of MBIs by telephone, with telephone vs. in-person interventions producing comparable outcomes (Bazarko et al., 2013; Gardner-Nix et al., 2008; Muller & Yardley, 2011). Therefore the six MBI sessions were delivered telephonically instead of in-person. In addition, the 2011 Pew Internet and American Life Project reports that approximately 87% of African Americans have cell phones, and that 73% of individuals who make less than \$10,000 per year have phones (U.S. Religious Landscape Survey, n. d.), providing support that the majority of persons with SCD are likely to have a phone.

The same MBI instructor delivered all MBI sessions. The instructor is a healthcare professional, and graduate of the Center of Mindfulness Professional Training Program from the University of Massachusetts. In total, the instructor has more than 10 years of instructional experience in mindfulness, two years experience teaching telephonic-based MBSR, as well as experience in leading groups for research studies.

Lastly, each 60-minute MBI session required patients to call a toll free 1-800 number. The toll free number did not require an access or login code, and could

accommodate up to 100 callers simultaneously, and can be accessed by telephone, internet, and mobile app (iOS and Android only). The conference service used was UberConference.

**Table 10 - Comparison between typical MBSR program and Telephonic MBI for persons with SCD used in this project**

Week	MBSR	Telephonic MBI
1	Body-scan 90-120 minutes	Mindful breathing 60 minutes
2	Breath awareness 90-120 minutes	Body scan 60 minutes
3	Sitting meditation, individual yoga 90-120 minutes	Loving Kindness 60 minutes
4	Stress coping 90-120 minutes	Mindful eating 60 minutes
5	Communication styles 90-120 minutes	Sensory Awareness 60 minutes
6	Yoga, sitting meditation, 0-120 minutes	Overview; conclusion 60 minutes
7	Loving Kindness 90-120 minutes	N/A
Retreat	Silent retreat 2-4 hours	N/A
8	Wrap up 90-120 minutes	N/A
MBSR = Mindfulness-based Stress Reduction; MBI = Mindfulness-based Intervention		

#### **4.2.8 Wait-listed Control Condition (Control)**

Patients randomized to the control condition did not receive the MBI, but received treatment as usual and were wait-listed. Treatment-as-usual consisted of standard

medication management as prescribed by their hematologist, primary care physician, psychologist, and or any other medical professionals overseeing treatment.

Wait-listed patients were offered the opportunity to crossover to the MBI condition once patients in the intervention arm completed six sessions. Patients that crossed over from wait-listed to MBI participated in the same protocol with patients randomized to future MBI groups.

## **4.2.9 Assessments**

### **4.2.9.1 Feasibility**

The first aim of this study was to determine feasibility and acceptability. Measures of feasibility were: (a) enrollment (number of participants consented and percent of participants recruited that were enrolled) and (b) randomization (percent of patients enrolled that were randomized). Participant level measures of feasibility included: (a) attendance (percent of each session attended by each MBI participant), (b) intervention completion (percent of total intervention sessions attended by each MBI participant), and (c) assessment completion (percent of completed patient-reported assessments at each time point). Failure to complete measures within 2 weeks of recruitment (baseline), or MBI Session 1, 3, and 6 resulted in missing data for that time point.

### **4.2.9.2 Acceptability**

Acceptability was assessed qualitatively. Semi-structured interviews were performed with nine randomly selected participants from the MBI condition, within two

weeks of the final MBI session by telephone, to assess acceptability and help interpret quantitative findings related to the exploratory aim (Creswell, 2003). Each MBI participant that completed at least one MBI session was randomly assigned a number, using the random number function in Microsoft Excel 2007 (Microsoft, Redmond, WA, USA), and then ordered in an ascending fashion. The participant with the smallest number was contacted first, followed by the second smallest. Two to three participants were selected from each of the four cohorts. Each interview was conducted by one study personal that was familiar with the content of the MBI. The interview consisted of the following questions:

- 1) Tell me about how easy or difficult it was for you to complete the weekly, telephone-based MBI sessions?
- 2) What impact, if any, do you feel the MBI program had on (a) your perceptions on chronic pain, and (b) your quality of life?
- 3) What did you find most useful about the MBI program?
- 4) What did you find least useful about the MBI program?
- 5) What would you want more of in the MBI program?
- 6) What would you eliminate or have less of in MBI program?
- 7) Tell me about how easy or difficult it was for you to practice mindfulness, and complete the homework assignments?
- 8) Do you intend to continue using this MBI?
- 9) Would you recommend a MBI to friends with SCD who also experience chronic pain?
- 10) Is there anything else that you would like me to know about your experience?

Because we were unable to find any literature on the subjective experiences of persons with SCD and chronic pain that participated in a mindfulness intervention, the guiding questions listed above were used to roughly structure conversations, allowing digression into other topics brought up by the participants. Interviews were digitally

recorded and lasted approximately 20 minutes.

#### **4.2.9.3 Demographic Assessment**

Socio-demographic data and clinical characteristics were self-reported by participants, and collected only at study enrollment (baseline). Participants were asked to report their gender, age, race, genotype, socioeconomic status, educational history, hospital utilization (e.g., self-reported number of ED visits and hospital admissions over the last two years), and disease-related complications (e.g., stroke, acute chest syndrome, vaso-occlusive crises). These items have been used to assess socio-demographic and clinical characteristics of persons with SCD in prior studies (Tanabe et al., 2013; Freiermuth et al., 2014).

#### **4.2.9.4 Efficacy**

To address Aim 2, five valid and reliable patient-reported questionnaires were administered to determine the effects of MBI relative to the control condition on pain catastrophizing, as well as pain interference and severity, depression, health-related quality of life (mental and physical health), and mindfulness (Table 11). Each questionnaire was administered at four time points: week 0 (baseline, prior to initiation of treatment), and weeks 1, 3, and 6. Assessments at weeks 1, 3, and 6 corresponded with MBI session 1, session 3, and session 6.

Participants had the option to complete each questionnaire via paper or as an online form. Participants that opted for paper forms were provided with a packet of questionnaire copies with return envelopes and stamps. Participants that opted for online

forms provided an email address, and were emailed hyperlinks that contained exact copies of the paper forms managed by redcap database (Harris et al., 2009). The order and structure of each measurement was identical between paper and online versions. Each assessment packet included the following five questionnaires (Table 11) for summary of instruments and schedule of assessments):

*Pain Catastrophizing Scale (PCS)* was used to assess pain catastrophizing. The PCS contains 13-items, rated on a 5-point scale, from 0 (not at all) to 4 (all the time). The total score for the PCS ranges between 0-52, with a higher score demonstrating more severe catastrophizing. In addition the PCS contains three subscales: helplessness (6 items), rumination (4 items), and magnification (3 items). The PCS was selected as the primary variable of interest in addressing intervention efficacy because it has been extensively studied across many different chronic pain populations, and is commonly used as a key outcome in determining the success of interventions that target chronic pain (Citero et al., 2007; Sullivan, 2009). A total PCS score of 30 represents clinically relevant level of catastrophizing, and corresponds to the 75th percentile of the distribution of PCS scores in clinic samples of chronic pain patients (Sullivan, Bishop, & Pivik, 1995). The PCS total score was the primary outcome.

*Brief Pain Inventory (BPI)* was used to assess physical pain. As one of the standard psychometric tools for clinical trials of pain (Turk et al., 2003), the BPI provides two sub-scales: pain interference and pain severity. Pain interference (7 items) and pain severity items (5 items) are rated on a 0-10 scale, with 10 indicating complete

interference or worst possible pain severity. There are no clinical cutoff scores for the BPI, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity, and the arithmetic mean of the seven interference items can be used as a measure of pain interference.

*Patient Health Questionnaire – 9 (PHQ-9)* was used to assess depression. The PHQ-9 is a multipurpose instrument used for screening, diagnosing, monitoring, and measuring severity of depression. Consisting of 9-items on a Likert scale (0 = not at all, 3 = nearly every day), the measurement provides a severity score depression (range 0-27) of minimal symptoms (5-9), minor depression (10-14), moderate depression (15-19), or severe depression (20-27).

*Patient-reported Outcomes Measurement Information System (PROMIS)* global short form was used to assess physical and mental health. The PROMIS global short form is a 10-item instrument that represents multiple domains, developed by the National Institute of Health. The tool has a total of 10 items, with Likert scales (0-5), and generates a global physical health score and a global mental health score. At this time there are no clinical cut-off scores for chronic pain via the PROMIS but are currently be developed (PROMIS, 2014).

*Mindful Attention Awareness Scale (MASS)* was used to assess mindfulness. The MASS measures present-moment awareness, interpersonal communication, thoughts, emotions, and physical states. Consisting of 15-items on a Likert scale (1= almost always

to 6= almost never), the measurement provides a single total score of mindfulness, with a higher score indicating higher levels of mindfulness.

**Table 11 - Instruments and Schedule of Assessments**

Instrument	Abbreviation	Domain	Scale/subscale Reliability – Chronbach alpha	Interpretation **	B	W1	W3	W6
Demographic Questionnaire	DEMO	Socio-demographic and clinical characteristics	n/a	n/a	X			
Pain Catastrophizing Scale	PCS	Pain Catastrophizing*	Total score .75 Rumination .87 Magnification .60 Helplessness .79	Low	X	X	X	X
Brief Pain Inventory	BPI	Pain interference and severity	Interference .89-.92 Severity .80-.87	Low	X	X	X	X
Patient Health Questionnaire – 9 item	PHQ-9	Depression	Total score 0.87	Low	X	X	X	X
Patient Reported Outcome Measurement Information System	PROMIS	Physical and Psychological Health	Mental and Physical 0.73-0.96	High	X	X	X	X
Mindful Awareness Attention Scale	MAAS	Mindfulness	Total score .87	High	X	X	X	X
* Primary outcome; **Scores representing “improved” functional health status; B=Baseline, W1 = Week 1								

### **4.3 Analytic Approach**

Atlas ti software (ATLAS.ti 7™, n.d.) was used to analyze qualitative data, and Statistical Analysis Software (SAS 9.3™, Cary, NC) was used to conduct statistical procedures for quantitative data, and to estimate effect sizes for the efficacy outcomes. When statistical significance testing was conducted, non-directional tests were performed with the level of significance set at 0.05. As noted earlier, the focus of this pilot study was to examine the direction and magnitude of effect of the MBI on primary and

secondary outcomes rather than conduct statistical significance testing.

#### **4.3.1 Sample Characteristics**

Descriptive statistics were used to summarize socio-demographic and clinical characteristics. Non-parametric Wilcoxon Two-Samples Tests were used to test for differences in continuous socio-demographic and clinical variables between conditions. Chi-square tests were performed to test for differences in categorical socio-demographic and clinical variables between conditions. A sensitivity analysis was performed to compare socio-demographic and clinical characteristics between randomized participants that completed at least one assessment at any time point to those that did not complete any outcome assessments (observable cases = no or yes).

#### **4.3.2 Feasibility**

Number (*n*) and percent (%) were used to summarize enrollment, randomization, assessment completion, intervention completion, and MBI session attendance. Additionally, the socio-demographic and clinical characteristics of those observable cases in the MBI condition that completed four or more intervention sessions were compared to those who completed less than four.

#### **4.3.3 Acceptability**

Acceptability was determined by qualitative analysis of semi-structured interviews, using an inductive data-driven approach. This allowed for extraction of core themes, as recommended for example by Hsieh and Shannon (2005) for cases when

theory or research literature is limited. Qualitative content analysis was selected because it is a widely and successfully used method for qualitative data analysis (Crowe et al., 2015). A multistage analytic strategy was developed for qualitative analysis: Step one; digital recordings were transcribed verbatim. Step two; transcripts were imported into Atlas ti software and then read and re-read by three study personnel familiar with the content of the MBI, and text passages that appeared to be relevant with regard to the research questions were extracted and coded, i.e. labeled as a term preferably close to the text passage itself. Further relevant text passages were sub-themed under an existing term, or assigned a new term whenever they did not fit into an existing category. In this style, the first two transcripts were coded. Step three; the emerging categories were reviewed and critiqued by the three study personal in a 60-minute group discussion and partially revised. Step four; the first two transcripts were re-coded, and the next two transcripts were coded based on adjustments to the coding scheme determined by the three coders. Step five; the three study personnel reassembled to discuss the first four interviews, and any new emergent codes. Step six; the remaining five interviews were coded.

#### **4.3.4 Efficacy**

Descriptive statistics were used to summarize the five measures at baseline, week 1, 3, and 6 for randomized participants with at least one outcome assessment completed (observable cases). Tables for unadjusted mean scores for each condition by time are presented. Random coefficients regression models (RRMs), a type of hierarchical mixed-

effects model for longitudinal data, were conducted to evaluate the trajectory of change in pain catastrophizing total scores and other pain-related outcomes. Non-linear temporal patterns were fitted as needed. The models were used to examine the pattern of change in each outcome over time and estimate effect sizes.

#### **4.4 Results**

The following sections describe (a) recruitment, enrollment, and randomization; (b) analysis sample characteristics; (c) assessment completion; (d) MBI session attendance; and (e) acceptability of study for the MBI participants. The efficacy of the MBI (N = 26) relative to control (N = 8) conditions on pain catastrophizing and other pain-related outcomes in observable cases was not conducted due to the small sample size of the control condition. Instead, trajectory analyses were conducted to evaluate the magnitude and pattern of change in the outcome measures over time in the MBI condition only.

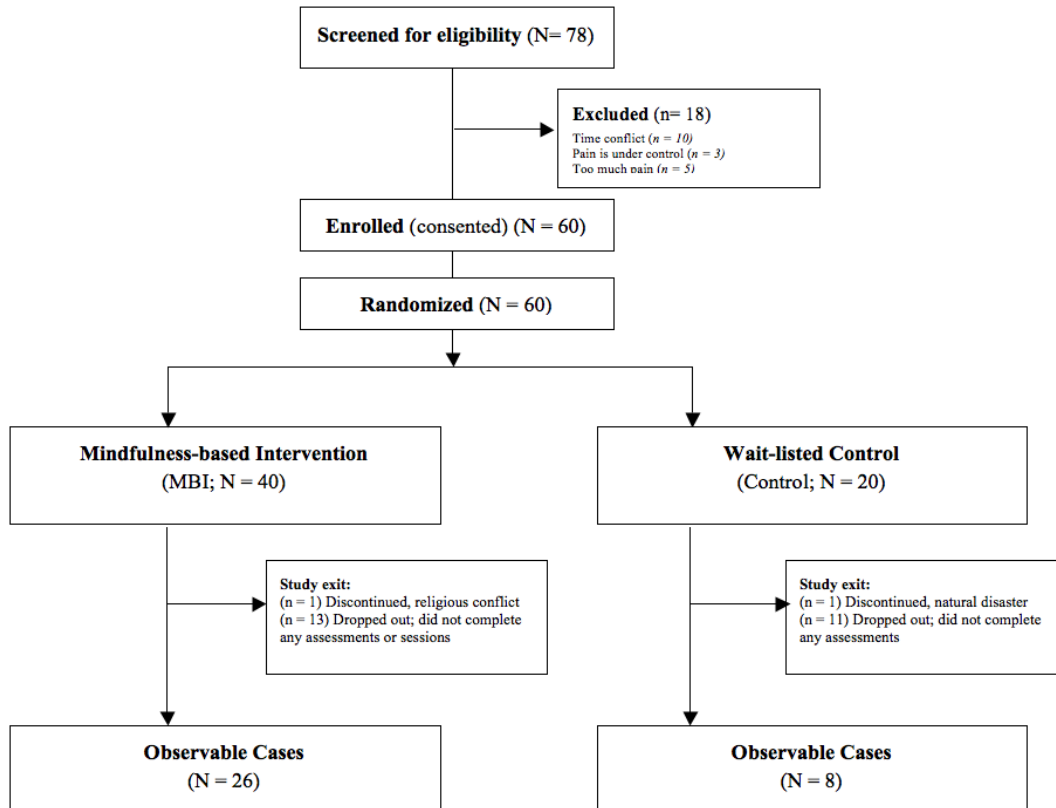
##### **4.4.1 Feasibility: Recruitment, Enrollment, and Randomization**

The consort diagram (Figure 3) details the number of patients with SCD and chronic pain who were recruited, enrolled, randomized to a treatment condition, as well as the reasons for study refusal. Additionally the figure indicates the number of observable cases, defined as randomized patients who completed at least one outcome assessment. From April 2015 to November 2015, 78 patients with SCD and chronic pain were approached, and 23% ( $n = 18$ ) declined to participate. All participants recruited

were recruited in-person at the SCD center, and no participants were recruited via mail. Of the 60 participants that were enrolled (consented), 100% were randomized to one of the two conditions (MBI,  $n = 40$ ; Control,  $n = 20$ ).

Figure 3 provides the reasons for study exit after randomization per condition. Among the 60 randomized participants, 43% ( $n = 26$ ) dropped out of the study before completing the baseline assessment. Within the MBI condition, 35% ( $n = 14$ ) dropped out and never attended any MBI sessions. One MBI participant withdrew due to religious conflicts, and the remaining 13 were lost to follow-up and could not be contacted. Of the 20 control participants, 60% ( $n = 12$ ) discontinued the study with 11 lost to follow-up that could not be contacted. The analysis sample included 34 observable cases (MBI,  $n = 26$ ; Control,  $n = 8$ ).

**Figure 3 - Study Consort Diagram**



#### 4.4.2 Analysis of Sample Characteristics

Baseline socio-demographic and clinical characteristics along with baseline outcome measures for the analysis sample and per condition are provided in Table 12. There were no significant differences between the MBI and control conditions in baseline characteristics. Among the 34 observable cases the average age was 36, 38% were male, 57% were SS genotype, 60% had either anxiety or depression, and the median number of ED visits and hospital admissions per person was approximately four. Mean baseline catastrophizing scores for the total sample ( $\mu = 18.8$ ) were below the 75<sup>th</sup> percentile of

distribution for chronic pain patients (non-clinically significant pain catastrophizing; Sullivan, 1995), while mean baseline depression scores indicated presence of clinically significant Major Depressive Disorder for the total sample ( $\mu = 10.0$ ) and MBI condition ( $\mu = 10.2$ ) (Manea, Gilbody, & McMillan, 2012).

A sensitivity analysis was performed to compare socio-demographic and clinical characteristics between analysis sample (observable cases;  $N = 34$ ) versus those that were randomized and excluded from the analysis sample (non-observable cases;  $N = 26$ ). Table 13 presents the results from the sensitivity analysis. The observable cases reported a significantly higher rate of Acute Chest Syndrome (65%) when compared to non-observable cases (27%,  $p < 0.01$ ). Additionally the observable cases had a significantly higher median number of ED visits (median = 4) over the past two years relative to non-observable cases (median = 2;  $p = .04$ ).

**Table 12 - Baseline Socio-demographic and Clinical Characteristics**

Characteristic	Statistics	Level	Group			P-value
			Total Sample N=34	MBI N=26	Control N=8	
<b>Sex</b>	N (%)	Male	13 (38.2)	11 (42.3)	2 (25.0)	0.44
<b>Genotype</b>		SS	21 (61.7)	15 (57.6)	6 (75.0)	0.46
<b>Anxiety or Depression</b>		Yes	20 (58.8)	17 (68.0)	3 (37.50)	0.21
<b>Yearly Household Income</b>		≤ 50k	14 (41.1)	10 (55.56)	4 (57.14)	1.000
<b>Education</b>		HS or lower	11 (32.3)	8 (40)	3 (37.5)	1.000
		College or higher	17 (50.0)	12 (60)	5 (62.5)	
<b>Employment</b>		Unemployed	22 (64.7)	17 (65.38)	5 (62.5)	1.000
<b>Insurance</b>		Medicare and or Medicaid	19 (55.8)	13 (68.42)	6 (75)	1.000
		Private or Other	8 (23.5)	6 (31.58)	2 (25)	
<b>Age</b>	N		34	26	8	0.26
	Mean (SD)		36.8 (12.4)	35.58 (12.02)	40.88 (13.68)	
	Median (25th, 75th)		34.5 (28, 45)	34 (27, 45)	39.5 (31, 49)	
	Min, Max		20, 65	20, 64	22, 65	
<b>ED visits per person</b>	N		34	25	6	0.35
	Mean		6.5 (7.6)	7.16 (8.19)	3.67 (3.39)	
	Median (25th, 75th)		4 (2, 8)	4 (2, 8)	3 (2, 4)	
	Min, Max		0, 30	0, 30	0, 10	
<b>Hospital Admissions per person</b>	N		34	25	8	0.53
	Mean		3.7 (4.2)	4.04 (4.54)	2.63 (2.72)	
	Median (25th, 75th)		3 (1, 5)	3 (1, 5)	3 (0, 3.5)	
	Min, Max		0, 16	0, 16	0, 8	
<b>Number of SCD related Complications</b>	N		34	26	8	

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Mean	2 (1.2)	1.88 (1.14)	2.38 (1.3)
Median (25th, 75th)	3 (1, 5)	1.5 (1, 3)	3 (1.5, 3)
Min, Max	0, 4	0, 4	0, 4

PCS Total Score	N	34	13	5	.692
	Mean (SD)	18.8 (13.6)	18.69 (14.74)	19.2 (11.65)	
	Median (25th, 75th)	16 (7, 24)	18 (7, 22)	14 (14, 24)	
	Min, Max	3, 51	3, 51	7, 37	
BPI – Pain Severity	N	34	13	4	.495
	Mean (SD)	4.5 (1.7)	4.71 (1.7)	3.96 (1.78)	
	Median (25th, 75th)	5.3 (3.5, 5.5)	5.25 (3.5, 6)	4 (2.4, 5.5)	
	Min, Max	1, 7.3	1, 7.25	2.33, 5.5	
BPI – Pain Interference	N	34	12	4	.671
	Mean (SD)	4.7 (2.2)	4.52 (2.4)	5.32 (1.24)	
	Median (25, 75)	4.9 (4.1, 6.2)	5 (2.7, 6.2)	4.86 (4.6, 6.1)	
	Min, Max	0, 7.9	0, 7.86	4.43, 7.14	
PROMIS – Physical	N	34	11	4	.456
	Mean (SD)	11.5 (1.6)	11.45 (1.86)	11.75 (0.96)	
	Median (25, 75)	11 (11, 12)	11 (10, 12)	11.5 (11, 12.5)	
	Min, Max	9, 16	9, 16	11, 13	
PROMIS – Mental	N	34	11	4	.791
	Mean (SD)	10.9 (2.2)	10.91 (2.34)	11 (1.83)	
	Median (25, 75)	11 (9, 12)	11 (9, 12)	11 (9.5, 12.5)	
	Min, Max	8, 27	8, 15	9, 13	
PHQ-9	N	34	12	4	.854
	Mean (SD)	10 (5.6)	10.25 (6.43)	9.25 (1.71)	
	Median (25, 75)	9.5 (7, 10.5)	9.5 (6, 11)	9.5 (8, 10.5)	
	Min, Max	3, 27	3, 27	7, 11	
MAAS	N	34	12	4	.145
	Mean (SD)	4.3 (1.3)	4 (1.36)	5.1 (0.57)	
	Median (25, 75)	4.3 (3.6, 5.4)	4.23 (2.8, 5.2)	5.33 (4.7, 5.5)	
	Min, Max	1.6, 5.7	1.6, 5.73	4.27, 5.47	

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Non-parametric p-values were calculated by the Wilcoxon Two-Sample Test for continuous variables and Fisher's Exact test for categorical; ED/admissions over 2 year period reported;

**Table 13 - Sensitivity Analysis: Observable versus Non-observable Cases**

Characteristic	Statistics	Level	Randomized with at least 1 assessment completed		P-value
			No N=26	Yes N=34	
Sex	n (%)	Male	15 (57.6)	13 (38.2)	0.19
Genotype		SS	15 (57.6)	21 (61.7)	0.46
		SC	9 (34.6)	10 (29.4)	
		SB+	2 (7.6)	3 (8.82)	
Anxiety or Depression		Yes	11 (42.3)	20 (60.6)	0.19
<b>Complications</b>					
Pulmonary Hypertension		Yes	5 (19.2)	7 (20.5)	1.00
Avascular necrosis		Yes	16 (61.5)	17 (50.0)	0.68
Acute Chest Syndrome		Yes	7 (26.9)	22 (64.7)	<b>&lt;0.01</b>
<b>Age</b>	Mean (SD)		38.19 (13.13)	36.82 (12.43)	0.77
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		36 (28, 45)	34.5 (28, 45)	
	Min, Max		23, 68	20, 65	
<b>ED visits</b>	Mean (SD)		4.27 (6.84)	6.48 (7.58)	<b>0.04</b>
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		2 (0, 6)	4 (2, 8)	
	Min, Max		0, 30	0, 30	
<b>Hospital Admissions</b>	Mean (SD)		2.54 (3.22)	3.7 (4.18)	0.15
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		1.5 (0, 5)	3 (1, 5)	
	Min, Max		0, 11	0, 16	
<b>Number of Complications Related to SCD</b>	Mean (SD)		1.85 (1.08)	2 (1.18)	0.711
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		2 (1, 2)	2 (1, 3)	
	Min, Max		0, 4	0, 4	

Non-parametric p-value is calculated by the Wilcoxon Two-Sample Test for continuous variables, and Fisher's Exact test for categorical variables; ED and Hospital admissions over the last two years.

#### 4.4.3 Feasibility: Assessment Completion

All 34 observable cases completed a demographic questionnaire. For each treatment condition, Table 14 presents the number of observable cases completing each questionnaire at each of the four time points. In terms of the baseline assessment, 42-50% ( $n = 11$  to 13) of the 26 MBI participants compared to 50-63% ( $n = 4$  to 5) of the 8 control participants completed each questionnaire. Approximately 62-69% ( $n = 16$  to 18) and 62-75% ( $n = 5$  to 6) of the MBI and control respectively completed each post-baseline questionnaire at each assessment.

**Table 14 - Completed Questionnaires for Observables Cases by Condition and Assessment (N=34)**

MBI (N=26)					
Questionnaire	Statistics	Baseline	Week 1	Week 3	Week 6
BPI	n (%)	13 (50)	17 (65.38)	17 (65.38)	16 (61.54)
MAAS		12 (46.15)	17 (65.38)	16 (61.54)	16 (61.54)
PCS		13 (50)	18 (69.23)	17 (65.38)	16 (61.54)
PHQ		12 (46.15)	17 (65.38)	16 (61.54)	16 (61.54)
PROMIS		11 (42.31)	17 (65.38)	16 (61.54)	16 (61.54)
Control (N=8)					
BPI	n (%)	4 (50)	6 (75)	6 (75)	6 (75)
MAAS		4 (50)	6 (75)	6 (75)	6 (75)
PCS		5 (62.5)	6 (75)	6 (75)	6 (75)
PHQ		4 (50)	6 (75)	6 (75)	6 (75)
PROMIS		4 (50)	6 (75)	5 (62.5)	6 (75)

BPI = Brief Pain Inventory; MAAS = Mindful Attention Awareness Scale ; PCS = Pain Catastrophizing Scale; PHQ-9 = Patient Health Questionnaire 9-item; PROMIS = Patient Reported Outcomes Measurement Information System;

Table 15 presents the number of questionnaires completed over the four assessment points for the 34 observable cases. For each questionnaire the median number of questionnaires completed ranged from 2.5 to 3.0 for the 26 MBI participants, while the median for the 8 control participants was 3.0. For the pain catastrophizing outcome, 53% ( $n = 14$ ) of the MBI participants and 87% ( $n = 7$ ) of the control participants completed at least three of the PCS questionnaires.

**Table 15 - Completed Number of Assessments (1-4) for Observable Cases (N=34)**

		MBI (n=26)			
Measurement	Statistics	1 Completed	2 Completed	3 Completed	4 Completed
BPI	n (%)	8 (30.7)	4 (15.3)	10 (38.4)	4 (15.3)
MAAS*		7 (26.9)	5 (19.2)	8 (30.7)	5 (19.2)
PCS		7 (26.9)	5 (19.2)	9 (34.6)	5 (19.2)
PHQ*		7 (26.9)	5 (19.2)	8 (30.7)	5 (19.2)
PROMIS*		7 (26.9)	5 (19.2)	9 (34.6)	4 (15.3)
		Control (n=8)			
BPI	n (%)	1 (12.5)	1 (12.5)	5 (62.5)	1 (12.5)
MAAS		1 (12.5)	1 (12.5)	5 (62.5)	1 (12.5)
PCS		1 (12.5)	0	6 (75.0)	1 (12.5)
PHQ		1 (12.5)	1 (12.5)	5 (62.5)	1 (12.5)
PROMIS		1 (12.5)	1 (12.5)	6 (75.0)	0

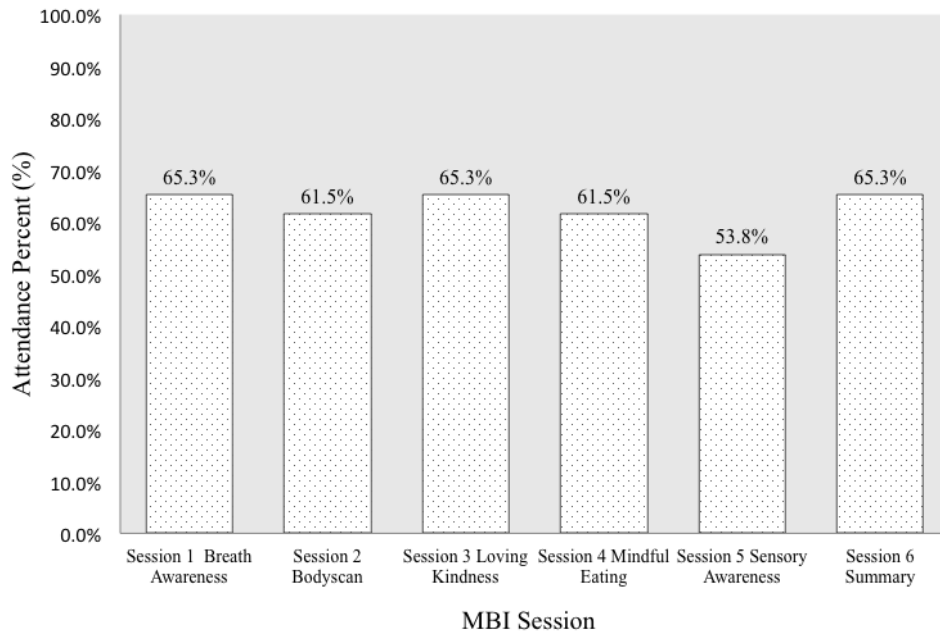
Interpretation: MBI condition (BPI assessment) –, 8 completed BPI one time, 4 completed it 2 times, 10 completed it 3 times, 4 completed it 4 times; BPI = Brief Pain Inventory; MAAS = Mindful Attention Awareness Scale ; PCS = Pain Catastrophizing Scale; PHQ-9 = Patient Health Questionnaire 9-item; PROMIS = Patient Reported Outcomes Measurement Information System; \*MAAS, PHQ, PROMIS do not add up to 26 for MBI condition due to one participant not completing any of those questionnaires and only completed BPI and PCS

#### 4.4.4 Feasibility: MBI Session Attendance

The 26 MBI participants attended a median of four sessions, with 57% ( $n = 15$ ) present at four or more of the six sessions. Table 16 summarizes the total number of MBI sessions attended by the 26 MBI participants. Three participants did not attend any MBI sessions and three others attended one session only. These six randomized participants were included as observable cases because they met the criteria of providing at least assessment. Figure 4 presents the percent of participants attending each session.

**Table 16 - MBI Total Session Attendance (N=26)**

Total Sessions Attended	n (%)
0	3 (11.5)
1	3 (11.5)
2	0 (0)
3	5 (19.2)
4	3 (11.5)
5	5 (19.2)
6	7 (26.9)



**Figure 4 - MBI Session Attendance (N=26)**

Table 17 further details session attendance for each session for each cohort. Each cohort had the potential of 10 randomized MBI participants. The total number of expected sessions to be attended was 156 for the 26 participants, of which 62% ( $n = 97$ ) were actually attended. Table 18 presents the socio-demographic and clinical characteristics of those observable cases in the MBI condition (N=15) that completed four or more intervention sessions were compared to those who completed less than four (N=19). Statistical significance testing was not performed due to the small sample sizes.

**Table 17 - MBI Session Attendance (N=26)**

Session / Skill	Cohort1 (n=6)	Cohort2 (n=5)	Cohort3 (n=7)	Cohort4 (n=8)	Total Participants N=26
	n	n	n	n	n (%)
1 / Breath Awareness	5	3	1	8	17 (65.3)
2 / Bodyscan	5	3	4	4	16 (61.5)
3 / Loving Kindness	4	4	4	5	17 (65.3)
4 / Mindful Eating	4	3	3	6	16 (61.5)
5 / Sensory Awareness	5	3	3	3	14 (53.8)
6 / Summary	6	3	3	5	17 (65.3)
	n (%)	n (%)	n (%)	n (%)	n (%)
Total Expected Sessions	36 (100)	30 (100)	42 (100)	48(100)	156 (100)
Total Attended Sessions	29 (80.5)	19 (63.3)	18 (42.8)	31 (64.5)	97 (62.1)

**Table 18 - Participant Characteristics by Session Completion**

Characteristic	Statistics	Level	Three or fewer sessions completed N=19	Four or more sessions completed N=15
Sex	n (%)	Male	6 (46.15)	5 (41.67)
Genotype		SS	11 (57.89)	10 (66.67)
		SC	6 (31.58)	4 (26.67)
		SB+	2 (10.53)	1 (6.67)
Anxiety or Depression Complications		Yes	11 (61.11)	9 (60)

Characteristic	Statistics	Level	Three or fewer sessions completed N=19	Four or more sessions completed N=15
Pulmonary Hypertension		Yes	6 (31.58)	1 (6.67)
Avascular necrosis		Yes	11 (57.89)	6 (40)
Acute Chest Syndrome		Yes	10 (52.63)	12 (80)
<b>Age</b>	Mean (SD)		38.26 (12.3)	35 (12.77)
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		37 (30, 47)	34 (26, 45)
	Min, Max		21, 65	20, 64
<b>ED visits</b>	Mean (SD)		8.63	4.2
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		4 (2.5, 11)	3 (2, 7)
	Min, Max		0, 30	0, 10
<b>Hospital Admissions</b>	Mean (SD)		4.94 (5.18)	2.2 (1.7)
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		3 (1, 8)	2 (1, 3)
	Min, Max		0, 16	0, 5
<b>Number of Complications Related to SCD</b>	Mean (SD)		2.11 (1.15)	1.87 (1.25)
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )		2 (1, 3)	1 (1, 3)
	Min, Max		0, 4	0, 4

#### 4.4.5 Acceptability:

Qualitative interviews were conducted with 34% of the observable MBI participants ( $n = 9$ ). This sample consisted of 75% ( $n = 6$ ) females, with a mean age of 38 years. At baseline, their average score was 11 points (SD 6.9, range 7 to 19) on the PCS, 7.3 points (SD 2.5, range 5 to 10) on the Patient Health Questionnaire, 12.3 points (SD 2.5, range 10 to 15) on the PROMIS - Mental, 11 points (OSD, range 11 to 12) on the PROMIS – Psychological, 4.6 points (SD 0.7, range 4.2 to 5.5) on the MAAS, and 5.3 (SD 1.6, range 3.5 to 6.5) on the BPI severity score.

In Table 19 the two overarching themes (intervention structure and intervention effect) that emerged from analysis, subdivided into five and six categories each, is described. Due to the semi-structured style of the interviews not every participant commented on every theme. Themes and categories are summarized below. Quotes in italics are presented for selected themes. Quotations pulled from the interviews have not been edited in order to retain the free, spontaneous nature of the participant responses.

**Table 19 - Overarching themes and categories that emerged from qualitative content analysis**

<b>Theme 1: Intervention Structure</b>		
<b>Category</b>	<b>Summary</b>	<b>Quotes</b>
<i>Communal</i>	Participants enjoyed the social context of the mindfulness intervention. They were able to converse with other persons with SCD and chronic pain, and listen to their experiences. The group setting reminded participants that they are not alone. Group conversations were helpful in generating ideas on how mindful exercises (e.g., breath awareness) could be implemented in their daily lives.	<p><i>“Yeah, I think that worked out really well, particularly the conference calls where we were all able to hear each other ... we were all able to have a discussion, have a conversation.”</i></p> <p><i>“The conference call is a good format. I think I like that more so than having to come to a place and be there in person. I was more comfortable in my own space.”</i></p>
<i>Remote</i>	The telephonic sessions were well received. Participants were able to hear each other’s voices, while being in the comfort of their own home, work office, or somewhere else. It was not difficult for participants to call in. Some patients would not have been able to participate due to work, disability/hospitalization, access to a care, or required childcare, if they were conducted in-person.	<p><i>“Oh it was very easy. It wasn’t difficult at all. I liked the fact that you could call in to a number. You could be anywhere you didn’t necessarily be at home. You know, there were days where I didn’t feel good but it didn’t matter because I was in the comfort of my home. I could be laying down, and most of the exercises required that, you know, you were in a relaxed position anyway. So it was very easy to complete.”</i></p> <p><i>“...one time I called in from a hospital, I was getting an ultrasound done and I called in from there. I’ve been in the car and I’ve called in. I’ve been home. So those were the three places.”</i></p>

<i>Reminders</i>	Participants appreciated individualized text, telephone, and email reminders the day of each mindfulness session. It made things easier for them to participate, because they did not have to try and remember when was the right time to call in, or what telephone number that they should be dialing in to. Overall patient's valued text and email reminders.	<i>"It was fairly easy. And also you were texting us to remind us, as a reminder. So that really helped when you texted everybody and had a number and stuff up with that information so that we could be reminded. So I thought that was really nice, and that helped."</i>
<i>Time</i>	Most patients believed that 1-hr per mindfulness session was appropriate, and enough time to go through specific concepts and meditation skills. Participants had varying opinions about what time the intervention should occur, but all agreed that afternoons were better than mornings. One participant wished that the classes had gone longer so more mindfulness techniques could have been learned.	<i>"I think that an hour was appropriate. It was enough time for the leader to go through the specific concepts and meditation types that we talked about."</i>
<i>Content</i>	There was general support for the content and exercises taught. Most of the exercises were viewed as useful, with the exception of the mindful eating exercise. Several participants commented that they did not have time to perform the mindful eating exercise. Another participant did not enjoy the loving kindness exercise, but was able to recognize how it could be helpful to others.	<i>"Everything was useful, you know, get that quality time to do it while I was at work, while she was talking through it."  "I really didn't find anything that was not really useful. I mean I thought it was a lot of great techniques. So I really didn't find anything that was not really useful."</i>
<i>Barriers</i>	Participants described very few barriers. When barriers were described, they were individual barriers and not 'general' barriers applicable to other participants. The most common barrier was timing of the intervention (e.g., selection of a weekday	<i>"Because of the time, I think, doing it later in the evening, would work better because 5:00 is when a lot of people are getting of work, or ... I think later in the day might work out better."</i>

	for that intervention to occur, and the specific time).	<i>“At first I had to eliminate everyone around me because sometimes my nephew comes over to my house and all that, and he’s noisy and all that. I just had to take a step back and think about getting alone to myself, like it requires you ... these exercises require you to be alone so you can get relaxed, so that’s what I did.”</i>
<b>Theme 2: Intervention Effects</b>		
<b>Category</b>	<b>Summary</b>	<b>Quotes</b>
<i>Pain</i>	MBI effects on pain were mixed. Patients described MBI impacting both acute and chronic types of pain. Two participants stated that the MBI was only helpful for acute pain, three participants described it as being helpful for acute and chronic pain, and one person described it as being somewhat helpful for generalized pain. Complete pain reduction was never achieved, but patients felt they were better equipped to make pain more tolerable by using mindful exercises.	<i>“But I’ve noticed that when I have spikes of pain, when it gets worse, being able to kind of sit down and calm myself and meditate has been helpful. Kind of like really acute episodes.”</i>  <i>“So I’ve always found that if I’m feeling stronger mentally, emotionally, I tolerate the pain better. So the classes offered certain specific techniques to help with that. So the quality of life is just better because of that. Because when you ... like 95% of my day is ... I’m in pain in some form or fashion. So being able to have tools that will keep my mind strong helps me tolerate and deal with the pain.”</i>
<i>Emotion Regulation</i>	Two negative emotions, anxiety and anger, were regulated more easily with mindfulness exercises. Patients described that when they begin to feel anxious or angry, they are able to focus on their breath, and calm themselves down. Mindfulness worked better for acute anxiety than chronic	<i>“Sure. It helped you not get angry quick. You know, it helped that. Take a deep breath.”</i>  <i>“During the daytime when somebody getting an attitude, you know, you step back – you know they always say take a</i>

	anxiety for one patient.	<p><i>deep breath and don't respond."</i></p> <p><i>"It would help you stay calm. It would help you get to know your body. And it will help you relax. Because people will blow up angry quick."</i></p>
<i>Undesired Outcomes</i>	An undesirable outcome was reported by a single participant: increased acute pain associated with the body-scan exercise. When this person practiced the body-scan exercise, and focused on a specific area of the body that was already hurting, the increased attention and focused awareness made the pain worse.	<i>"There was one, the body scan, wasn't helpful to me. It's focusing on the area where the pain is coming from, for me personally, isn't helpful. It makes it worse. For me to focus on the breath is definitely helpful."</i>
<i>Practice and Comprehension</i>	All participants stated that they would continue practicing mindfulness after study, and would recommend a MBI program to others with SCD and chronic pain. A variety of locations were described for where participants practiced mindfulness, when they practiced, and with whom they practiced with. Most participants practiced the mindfulness exercises at home or at work, usually in the morning or evening, and typically by themselves. There was a combination of mindfulness comprehension and misinterpretation. Some participants were able to articulate a basic understanding of mindfulness, while others perceived mindfulness as a type of distraction mechanism, and focused on intentionally blocking out negative sensations from their awareness.	<p><i>"I incorporate it every night where right before I go to bed, I'm already laying down, and I'm scanning where I'm hurting. Because at night you focus more on the pain because you don't have anything else to do."</i></p> <p><i>"I think that it changed my perspective because a lot of times when I am in pain I am totally focused on that pain, so this helped me do exercises where I'm not just focused on my pain. I can kind of work through it a little bit and do other things besides just focus on the pain."</i></p>
<i>Modifications</i>	Because most participants were pleased	<i>"The way the program is set up now is</i>

	<p>with the intervention design and content, there were few suggestions regarding how the intervention could be modified. Some modifications suggested included the inclusion of teenagers and younger individuals with SCD, adding 'levels' to the intervention that a participant can progress through, and the addition of visualization exercises.</p>	<p><i>really great. What I would like to see is if there was, you know, like levels. Like this one was Level 1. And Level 2 would be like, for example, you take the breathing exercises and you incorporate that with some type of physical therapy kind of situation, where, you know ..."</i></p> <p><i>"I don't see how you can make it better. The only thing I said, the only one I didn't ... [mindful eating exercise] it wasn't that I didn't like it, I'm just an overeater, and that's something I got to fix."</i></p>
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#### 4.4.6 Preliminary Efficacy

Descriptive statistics for pain catastrophizing as well as pain interference and severity, depression, health-related quality of life (mental and physical health) and mindfulness are presented in Tables 20 through 22 for the observed cases in the MBI and control conditions at each time point.

The results of the trajectory analyses using RRM to evaluate the magnitude and pattern of change in each outcome over time in the MBI condition only are presented in Table 23. The model included the fixed effects of time as well as the random effects of participant and participant by time. Each model was evaluated for quadratic temporal effects; however, a linear model best fit the data for each outcome. The impact of the MBI over time was most evident in the PCS - Magnification ( $p = .07$ ) and PROMIS - Mental ( $p = .05$ ) sub-scale scores. These results, however, should be interpreted with caution because the estimated trajectories are based on small sample sizes with a high rate of missingness.

Table 24 presents the adjusted means for each outcome as well as Cohen  $d$  effect sizes. The means are adjusted for fixed and random effects included in each model. Each effect size represents the magnitude of the within-participant change in the adjusted means from baseline to week 6 for each outcome, applying Morris and DeShon's (2002) correction method for dependence between means. Although not statistically significant, a large effect size was observed for pain catastrophizing measure (Cohen's  $d = 1.13$ ). The effect size was 1.13 for PCS - Magnification and -3.53 for the PROMIS - Mental,

indicating large effect sizes. Observed effect sizes indicate medium to large effects for several outcomes. However a larger sample size is needed to obtain reliable and stable estimates of effect for these outcomes. Figure 5 shows the change over time for these two outcomes.

**Table 20 - Unadjusted Means for Catastrophizing Outcomes**

Catastrophizing	Statistics	MBI				Control			
		Baseline	Week1	Week3	Week6	Baseline	Week1	Week3	Week6
PCS Total Score	N	13	18	17	16	5	6	6	6
	Mean (SD)	18.69 (14.74)	22.5 (13.56)	20.29 (10.17)	16.69 (12.4)	19.2 (11.65)	16 (5.18)	16.5 (7.48)	15.67 (8.73)
	Median (25, 75)	18 (7, 22)	25.5 (13, 32)	21 (16, 26)	13 (6.5, 24)	14 (14, 24)	16 (11, 17)	13.5 (12, 20)	13 (10, 15)
	Min, Max	3, 51	1, 49	2, 35	3, 43	7, 37	11, 15	10, 30	10, 33
PCS Helplessness	N	13	18	17	16	5	6	6	6
	Mean (SD)	7.69 (6.33)	9.11 (6.82)	7.65 (4.58)	6.88 (5.99)	6.8 (5.4)	6.5 (2.43)	6.5 (3.27)	5.67 (3.33)
	Median (25, 75)	6 (3, 8)	10 (2, 13)	7 (5, 12)	4.5 (3, 9)	5 (4, 9)	6 (5, 7)	6 (4, 8)	5 (3, 6)
	Min, Max	1, 23	0, 24	1, 14	1, 22	1, 15	4, 11	3, 12	3, 12
PCS Magnification	N	13	18	17	16	5	6	6	6
	Mean (SD)	4.15 (3.98)	5.56 (2.97)	4.53 (2.55)	3.75 (2.79)	4.2 (2.28)	3.5 (1.38)	3.5 (2.35)	3.67 (1.63)
	Median (25, 75)	3 (1, 6)	6 (3, 7)	5 (3, 6)	3 (1.5, 5.5)	4 (3, 4)	3 (3, 4)	2.5 (2, 4)	3 (3, 3)
	Min, Max	0, 12	1, 10	0, 8	0, 9	2, 8	2, 6	2, 8	3, 7
PCS Rumination	N	13	18	17	16	5	6	6	6
	Mean (SD)	6.85 (5.1)	7.83 (4.7)	8.12 (3.9)	6.06 (4.3)	8.2 (4.15)	6 (2)	6.5 (2.17)	6.33 (4.41)
	Median (25, 75)	6 (2, 12)	8.5 (5, 13)	8 (6, 11)	4 (3.5, 9)	6 (6, 11)	6 (5, 8)	6 (5, 8)	4.5 (2, 9)
	Min, Max	1, 16	0, 15	1, 15	1, 15	4, 14	3, 8	4, 10	2, 14

PCS = Pain Catastrophizing

**Table 21 - Unadjusted Means for Behavioral Outcomes**

Behavioral Outcomes	Statistics	MBI				Control			
		Baseline	Week1	Week3	Week6	Baseline	Week1	Week3	Week6
PHQ-9	N	12	17	16	16	4	6	6	6
	Mean (SD)	10.25 (6.43)	11.53 (5.6)	10.69 (5.96)	8.88 (6.53)	9.25 (1.71)	7.83 (4.36)	8.83 (3.87)	7.83 (3.25)
	Median (25, 75)	9.5 (6, 11)	11 (6, 16)	12 (5.5, 14)	8 (4, 10.5)	9.5 (8, 10.5)	7.5 (4, 12)	9.5 (6, 11)	7 (6, 10)
	Min, Max	3, 27	3, 21	2, 21	1, 22	7, 11	3, 13	3, 14	4, 13
PROMIS – Mental	N	11	17	16	16	4	6	5	6
	Mean (SD)	10.91 (2.34)	11.82 (3.09)	11.69 (2.75)	12.31 (2.06)	11 (1.83)	11.67 (2.42)	10.4 (1.95)	10.5 (2.43)
	Median (25, 75)	11 (9, 12)	13 (9, 15)	12.5 (9.5, 14)	12 (11, 14)	11 (9.5, 12.5)	11 (10, 14)	9 (9, 12)	9.5 (9, 13)
	Min, Max	8, 15	5, 15	7, 16	9, 16	9, 13	9, 15	9, 13	8, 14
MAAS	N	12	17	16	16	4	6	6	6
	Mean (SD)	4 (1.36)	4.13 (0.96)	4.13 (0.96)	4.13 (0.92)	5.1 (0.57)	4.79 (0.32)	4.22 (1.05)	4.49 (0.85)
	Median (25, 75)	4.23 (2.8, 5.2)	3.93 (3.4, 4.7)	3.87 (3.3, 5)	4.13 (3.4, 4.7)	5.33 (4.7, 5.5)	4.87 (4.6, 4.9)	4.17 (3.6, 5.1)	4.6 (3.8, 5)
	Min, Max	1.6, 5.73	2.67, 5.67	2.67, 5.67	2.73, 5.6	4.27, 5.47	4.27, 5.2	2.8, 5.53	3.33, 5.6

PHQ9 = Patient Health Questionnaire 9 item; PROMIS = Patient Reported Outcomes Measurement Information System – Mental Subscale;

MAAS = Mindful Attention Awareness Scale

**Table 22 - Unadjusted Means for Physical Outcomes**

Physical Outcomes	Statistics	MBI				Control			
		Baseline	Week1	Week3	Week6	Baseline	Week1	Week3	Week6
PROMIS – Physical	N	11	17	16	16	4	6	5	6
	Mean (SD)	11.45 (1.86)	11.35 (2.32)	11.56 (2.06)	12.06 (2.86)	11.75 (0.96)	12.83 (3.13)	11.6 (1.82)	11 (2.76)
	Median (25, 75)	11 (10, 12)	12 (10, 13)	12 (9.5, 13)	12 (10.5, 13.5)	11.5 (11, 12.5)	14 (9, 15)	11 (10, 13)	11 (9, 14)
	Min, Max	9, 16	8, 15	8, 15	6, 18	11, 13	9, 16	10, 14	7, 14
BPI – Pain Severity	N	13	17	17	16	4	6	6	6
	Mean (SD)	4.71 (1.7)	3.51 (1.45)	4.43 (1.95)	4.44 (2.66)	3.96 (1.78)	4.63 (1.39)	5 (0.79)	4.38 (1.24)
	Median (25, 75)	5.25 (3.5, 6)	3.25 (2, 4.5)	4 (2.8, 6)	4.13 (2, 6.5)	4 (2.4, 5.5)	4.5 (3.8, 5)	4.63 (4.5, 6)	4.38 (3, 5.5)
	Min, Max	1, 7.25	1.75, 5.75	1.75, 8.5	0, 8.25	2.33, 5.5	3, 7	4.25, 6	3, 6
BPI – Pain Interference	N	12	17	17	16	4	6	6	6
	Mean (SD)	4.52 (2.4)	4.8 (2.33)	4.62 (1.86)	4.11 (2.33)	5.32 (1.24)	3.64 (1.38)	5.1 (0.74)	4 (1.74)
	Median (25, 75)	5 (2.7, 6.2)	4.57 (3.3, 6.3)	5 (3, 5.9)	3.93 (2.4, 6.1)	4.86 (4.6, 6.1)	3.86 (2.4, 4.9)	5.29 (4.4, 5.6)	4.14 (3.1, 4.9)
	Min, Max	0, 7.86	0.14, 8.43	1.14, 8.14	0.43, 8	4.43, 7.14	1.86, 5	4, 6	1.29, 6.43

PROMIS = Patient Report Outcomes Measurement Information System – Physical Subscale; BPI = Brief Pain Inventory;

**Table 23 - Random Coefficients Regression Model Results (RRM; N=26)**

	Time				
	<i>b</i>	SE	F	df	<i>p</i>
PCS - Total Score	-1.41	1.08	1.70	1, 18	.20
PCS - Rumination	-0.17	.41	.18	1, 18	.67
PCS - Helplessness	-0.71	.48	2.14	1, 18	.16
PCS - Magnification	-0.49	.25	3.68	1, 18	<b>.07</b>
BPI - Interference	-0.16	.19	.76	1, 17	.39
BPI - Severity	.06	.17	.14	1, 17	.71
PROMIS - Mental	.32	.15	4.38	1, 17	<b>.05</b>
PROMIS - Physical	.25	.21	1.34	1, 17	.26
PHQ-9 - Total Score	-0.49	.57	.72	1, 17	.40
MAAS - Total Score	.04	.10	.20	1, 17	.66

The models include the observable cases assigned to the MBI condition only. PCS = Pain Catastrophizing Scale; PROMIS = Patient Report Outcomes Measurement Information System; MAAS = Mindful Awareness Attention Scale; BPI = Brief Pain Inventory; PHQ = Patient Health Questionnaire 9-item; *b* = standardized regression coefficients; SE = standard error; df = degree of freedom; F = Type III Fixed Effects of time.

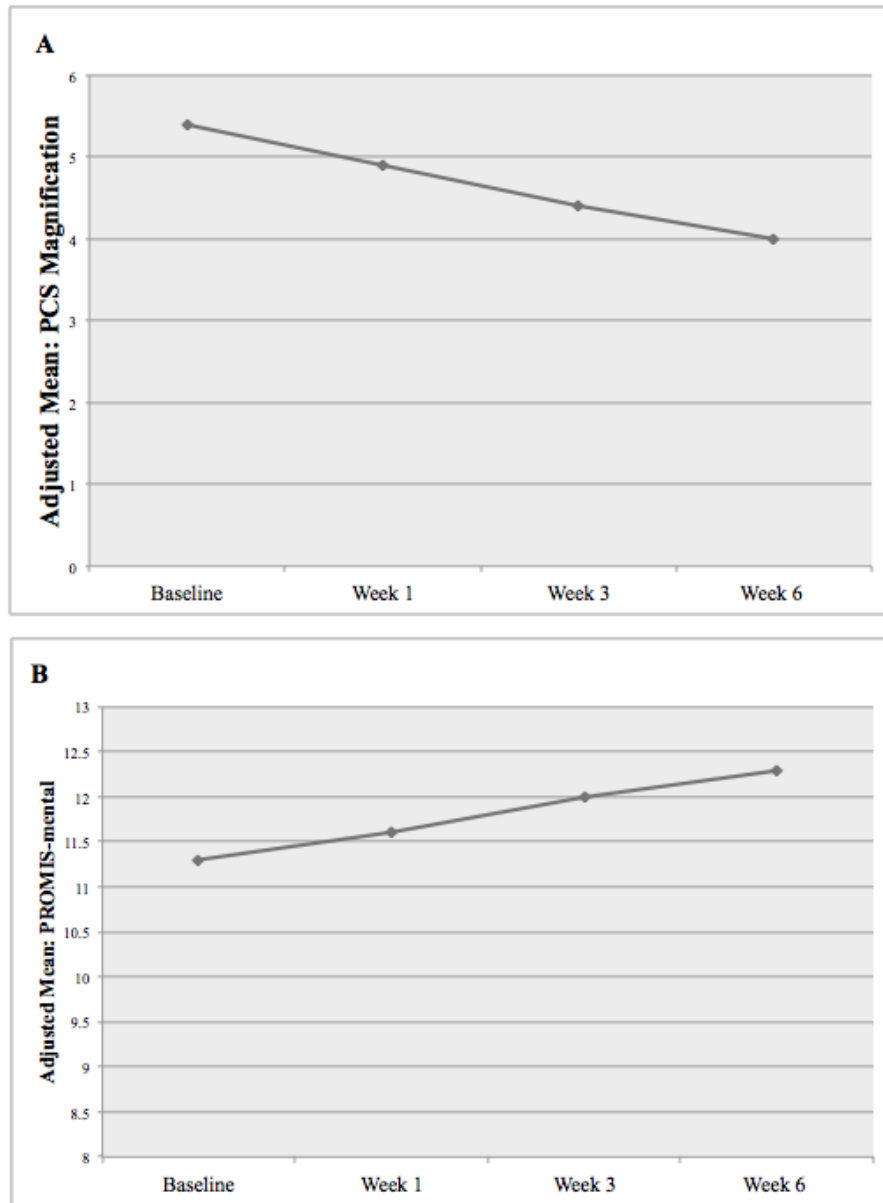
**Table 24 - Random Coefficients Regression Models: Adjusted Means**

Physical Outcomes	Statistics	MBI (N=26)				Cohen's <i>d</i>
		Baseline	Week 1	Week 3	Week 6	
PCS - Total Score	Mean (SD)	22.2 (10.9)	20.8 (9.5)	19.3 (8.1)	17.9 (7.0)	1.13
PCS - Rumination	Mean (SD)	7.8 (3.6)	7.6 (3.2)	7.4 (3.0)	7.3 (2.9)	0.25
PCS - Helplessness	Mean (SD)	8.9 (5.0)	8.2 (4.4)	7.5 (3.7)	6.8 (3.1)	2.11
PCS - Magnification	Mean (SD)	5.4 (2.9)	4.9 (2.4)	4.4 (2.0)	4.0 (1.5)	2.25
BPI - Interference	Mean (SD)	4.9 (1.6)	4.7 (1.5)	4.5 (1.4)	4.4 (1.4)	0.16
BPI - Severity	Mean (SD)	4.2 (0.9)	4.3 (1.1)	4.4 (1.4)	4.4 (1.6)	-1.13
MAAS - Total Score	Mean (SD)	4.0 (0.9)	4.1 (0.7)	4.1 (0.7)	4.1 (0.7)	-0.14
PHQ-9 - Total Score	Mean (SD)	11.6 (4.6)	11.1 (4.2)	10.6 (4.2)	10.1 (4.6)	0.37

PROMIS – Physical	Mean (SD)	11.1 (0.8)	11.4 (1.0)	11.6 (1.2)	11.9 (1.4)	-5.14
PROMIS – Mental	Mean (SD)	11.3 (2.3)	11.6 (2.1)	12.0 (1.9)	12.3 (1.7)	-3.53

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PCS = Pain Catastrophizing Scale; PROMIS = Patient Report Outcomes Measurement Information System; MAAS = Mindful Awareness Attention Scale; BPI = Brief Pain Inventory; PHQ = Patient Health Questionnaire 9-item; Cohen's *d* = effect size for within-participant change in scores from baseline to week 6.



PCS = Pain Catastrophizing Scale; PROMIS = Patient Report Outcomes Measurement Information System;

**Figure 5 - Means for Adjusted PCS and PROMIS Scores**

## ***4.5 Discussion***

The goal of this pilot randomized controlled clinical trial (RCT) was to explore the feasibility and acceptability an abbreviated 6-session MBI that was targeted for persons with SCD and chronic pain, and to obtain preliminary data on the efficacy of this intervention relative to a wait-listed control condition on pain catastrophizing and other pain-related outcomes. Our preliminary findings suggest that an abbreviated MBI is feasible and acceptable for persons with SCD and chronic pain, and may have potential benefits on pain catastrophizing and other pain-related outcomes.

### **4.5.1 Recruitment, Enrollment, and Randomization**

We did not experience difficulties with participant recruitment or enrollment, despite that 100% of participants were African American and the majority had never heard of a MBI. This is surprising because recruitment of minority participants has proven to be a challenge for many clinical trials (Paskett et al., 2008). In addition, the recruitment of African Americans into clinical trials has been historically difficult because of their mistrust of researchers (e.g., Tuskegee syphilis experiment; CDC, 2015) and poor experiences within the healthcare system (Paskett et al., 2008). Our positive experience with recruiting a predominately minority sample is not unique. Other MBI studies that have recruited *only minority* samples, and have not reported recruitment difficulties include traumatized minority and refugee groups (Hinton et al., 2013), African American women with PTSD and a history of intimate partner violence (Dutton et al., 2013), and ethnic minorities with substance use disorders (Witkiewitz et al., 2013).

Of the two recruitment strategies, in-person and by mail, only in-person recruitment was found to be feasible. In-person recruitment was extremely successful with 77% of approached participants choosing to enroll in the study. One difficulty encountered with in-person recruitment was limited recruitment time. Patients recruited in the clinic were approached either immediately before their appointment or immediately after their appointment was over. In both scenarios there was a limited amount of time to build rapport with each patient, explain the study, discuss inclusion and exclusion criteria, review the consent form, and provide additional study details. No participants were recruited or enrolled into the study by mail. Recruitment letters were mailed every other week yet no patients were successfully enrolled through mail. Recruitment of minority and vulnerable populations by mail may or may not be feasible. Mail may be more efficacious for African Americans who have middle or high socioeconomic status (SES) than those who have low SES (Yancy et al., 2006). In-person recruitment continues to be the primary and most effective method for recruitment of minority populations in clinical trials and observational studies (Yancy et al., 2006). Because the majority of SCD participants in our MBI study had annual household incomes less than \$50,000 and were not college educated, recruitment by mail may not have been a feasible.

#### **4.5.2 MBI Attendance and Retention**

The MBI attendance rate, approximately 57% of participants completing at least four mindfulness sessions, was deemed acceptable for this sample. In the clinical

environment (e.g., out-patient clinic), non-adherence rates for appointments by persons with SCD have been reported as high as 47% (Robinson et al. 2006). Non-adherence to scheduled appointments has been associated with gender, developmental period, minority status, history of previously missed appointments, and low SES (Crosby et al., 2009).

Additionally, attendance rates of 50% or less have been well documented for chronic pain samples enrolled in MBI and non-MBI interventions. A recent literature review reported MBI dropout for persons with chronic pain to be between 2-50%, with loss to follow-up ranging from 8% to 52% (Bawa et al., 2015). Other non-MBI and remote-interventions, such as exposure therapy (designed to help patients approach feared and avoided trauma-related material through *in vivo* and imagined exposure), and remotely delivered web-based interventions have also suffered low intervention attendance (Zayfert et al., 2005; Brady et al., 2001; Christensen et al., 2009). One hypothesis as why persons with pain are unable to attend, or choose not to attend sessions is because of an exaggerated, pain-related fear of participation (fear-avoidance model; Vlaeyen and Linton, 2000). Based on the fear-avoidance model, some persons with SCD and chronic pain may be afraid of additional exposure to pain or pain-related feelings that a MBI session may elicit.

### **4.5.3 Assessment Completion**

Missing data is ubiquitous throughout clinical trials, and this study was no exception. Despite having proactive strategies to safeguard against missing baseline, week 1, 3, and 6 assessments (e.g., weekly telephone, text, email reminders; three

monetary payments; choice between online or paper submissions) there was still a significant amount of missing data. Missing data is expected for longitudinal studies (Ibrahim & Molenberghs, 2009), and numerous methods for handling missing data have been examined and implemented (Verbeke and Molenberghs 2000).

The amount of missing data was undesirable (MBI condition, 40%; control condition, 25%), but falls within the range of expected missing outcome data for a RCT conducted within a clinical population. A review of RCTs published in top medical journals (e.g., British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine) found that the percentage of participant missing data ranged from 0% to 70% (Bell et al., 2014). Other longitudinal studies with SCD patients have encountered similar difficulties, with moderate to large amounts of missing or incomplete self-report data (Gil et al., 2000, 2004; Keller et al., 2014). At this time there is no solution to prevent missing data but there are cognitive techniques (e.g., Motivational Interviewing) and statistical approaches (e.g., Intention-to-treat analyses [ITT], multiple imputations [MI], maximum-likelihood [ML]) that can be used to decrease the frequency and impact of missing data (Bell et al., 2014).

#### **4.5.4 Acceptability**

Our experience of delivering each MBI session remotely by phone was positive. Telephonic delivery of the MBI was convenient for patients that lacked means of transportation, removed travel time to and from a clinic, and provided additional flexibility to patients that were employed or had other responsibilities that required their

physical presence. No patient refused or was ineligible to participate because they did not have cellphone or access to a telephone. If the study were not conducted by phone many of the patients that did enroll would not have been able to due to a lack of transportation. In general, patients perceived the telephonic MBI as acceptable, easy to access, and consume.

Telephonic therapies have been successfully used in other chronic diseases to treat depression, anxiety, and illness-specific symptoms. For instance, meta-analyses of telephone delivered cognitive behavioral therapy (CBT) have shown improved health outcomes (Muller & Yardley, 2011), demonstrated non-inferiority with in-person CBT, and have shown lower attrition rates than face-to-face psychotherapy (Wierbicki & Perarik, 1993). And other telephone-delivered therapies such as dialectical behavioral therapy, acceptance and commitment therapy, and mindfulness-based cognitive therapy for depression have also been shown to be feasible and acceptable approaches for symptom management (Ost, 2008).

In SCD, we are unaware of any studies that have investigated the acceptability of a remotely delivered intervention for pain. Smartphones in SCD have been previously used to remotely monitor pain and symptoms (Jacob et al. 2012, 2013; Shah et al., 2014), facilitate patient-provider communication (Jacob et al., 2013), and provide home-based symptom management (McClellan et al., 2009). To our knowledge this is the first study that demonstrates the acceptability of a telephonically conducted intervention for pain in persons with SCD.

The modifications made to our telephonic MBI curriculum are congruent with recommendations made by Dobkin and colleagues (2014) in how the original MBSR program content should be adapted for a specific patient population. The telephonic MBI format was reordered from the original MBI content (Table 10) to allow the original content and teachings to be believed by teleconference in six weeks instead of eight, and 60 minutes instead of 120 minutes.

Lastly, the telephonic MBI was found to be acceptable for persons with SCD and chronic pain that reported more medical complications. As shown by the sensitivity analysis (Table 13) participants who completed at least one assessment had more reports of Acute Chest Syndrome, visits to the ED, and hospital admissions than those who did not complete at least one assessment. It may be that participants with more complications had higher intrinsic motivation to participate and complete the study (e.g., a attempt to better manage their disease and symptoms) than those with fewer reported complications (Ryan & Deci, 2000; Ryan, Plant, & O'Malley, 1995).

#### **4.5.5 Efficacy**

The results of the trajectory analyses used to evaluate the magnitude and pattern of change in each outcome over time should be interpreted with caution. The study was not powered to conduct statistical testing. As previously stated, forty patients were randomized to the MBI condition, 14 were excluded, and only 26 observable cases were left for analysis. Additional sub-analyses (e.g., high versus low catastrophizers, high versus low session attendance) were not conducted due to the high likelihood of

committing a statistical error due to small sample size, lack of power, and limited degrees of freedom. To reduce assessment missingness RRM's were performed with and without multiple imputation (x40 imputations). Because RRM's with and without multiple imputation yielded similar results, trajectories without multiple imputations were presented in the results.

Despite being underpowered all of the RRM's trended in the right direction, and two of the subscales (PCS – Magnification; PROMIS – mental) approached statistical significance. As the primary efficacy outcome, we expected a statistically and clinically significant decrease in PCS of approximately 30% (Younger, McCue, & Mackey, 2009). It may be due to the small sample size, degree of missing data, and lack of weekly and follow-up assessments (e.g., week 1 through week 6; post-intervention 3 & 6 month assessments) that we were unable to capture a larger improvement in PCS. Furthermore the RRM data for each efficacy outcome appeared to be trending toward a quadratic model. In the literature quadratic effects are commonly reported in MBI studies (Laurent et al., 2013; Mackenzie et al., 2013; Arch & Ayers, 2013) and had our sample been larger a significant quadratic effect may have been found. Quadratic treatment effects are believed to occur due to increased sensory awareness, and attention toward negative or uncomformable stimuli during the initial sessions (increased negative scores; increased slope), followed by decrease in scores after adapting mindful techniques (decrease negative scores; decreased slope). Interestingly there was no quadratic or linear treatment effect for mindfulness (MAAS). Because most participants stated that they had

never heard of mindfulness before enrolling in the study, we expected very low mindfulness scores at baseline but significantly higher scores at Week 6. This did not occur. Other MBI studies have reported moderate to large effect sizes for MAAS with  $p < .01$  (Smith et al., 2006; Roemer et al., 2008). It could be that participants did not have enough exposure to fully comprehend mindfulness constructs because of the 60-minute duration of each telephone call, or because they were all ‘beginners’. Therefore low mindfulness scores may not necessarily reflect an actual lower state of mindfulness, but reflect their novice or entry-level understanding of its core concepts (de Bruin, et al., 2011).

Reported treatment effect sizes (Table 24) should also be interpreted cautiously. The direction of each effect size is in the right direction, and the majority of the effect sizes are moderate to large suggesting a strong MBI effect. But due to the small sample size these effect sizes may be unreliable and biased toward overestimating the true effect size.

#### ***4.6 Limitations***

This study has several major limitations. First and foremost the study was underpowered, making it difficult to detect differences and generate accurate and reliable effect size estimates. In addition to being underpowered, there was a high degree of missing data that further weakened our ability to detect significant changes in efficacy outcomes. A third limitation was our control condition was a non-active control condition that also suffered a high degree of missing data. Due to the few number of observable

cases in the control condition, it was not possible to conduct trajectory analyses for the control condition or thus compare trajectories between conditions. Forth, the timing of the MBI interventions was not standardized across cohorts. Due to the MBI instructor's availability we were not able to standardize the day of the week the MBI session was conducted, or the start and stop time across the MBI cohorts. Ideally each MBI cohort would have started on the same day of the week (e.g., Wednesday) and at the same time (e.g., 5:00pm). Additional limitations include a high number of missing baseline assessments, lack of weekly assessments (e.g., missing Week 2, Week 4) and post-intervention follow-up (e.g., 3 month, 6 month). Because we did not collect assessments at each week it is possible that significant intervention effects may not have been not captured. Lastly, the time window in which assessments were collected was extremely lenient. In other remote MBI studies, assessments are typically collected immediately following a MBI training session (Klatt et al., 2009; Ouweneel et al., 2012) versus participants in our study were given up to a week to complete their assessments.

#### ***4.7 Recommendations***

There are several recommendations that can be proposed to improve the design of this study (Table 25). First and foremost a non-active control condition should not be used. Future studies should be sure to incorporate an active control condition, such as a sham-mindfulness control to sustain participant involvement in the study (Zeidan et al., 2015). Second, only participants that have returned a baseline assessment should be randomized. Randomizing only participants that complete a baseline assessment will

provide a minimum of one assessment per participant. Third, Motivational Interviewing (MI) could be used a technique to increase intrinsic motivation of MBI participants. Motivational Interviewing is a powerful, efficacious tool that has been used to increase treatment engagement and retention in a variety of clinical settings and populations (Burke et al., 2003; Carroll et al., 2006; Hetttema et al., 2005; West et al., 2007). We are unaware of any behavioral or cognitive studies that have implemented MI for persons with SCD. Forth, relapse-prevention techniques could be implemented into the MBI design (e.g., incorporated into individual MBI sessions). A relapse-prevention strategy would attempt to decrease the likelihood of relapse into pain behavior (e.g., pain catastrophizing) by the participant (Naylor et al., 2008). Persons with SCD are idea candidates for a strategy like this due to the frequency of vaso-occlusive crises, and frequent ED visits and hospital admissions that could elicit a relapse of negative pain behavior. Two additional changes that could be implemented to possibly increase participant retention and study involvement are individually tailored MBI sessions (individual versus group sessions; focus on patient-selected strategies), and patient co-run sessions (e.g., a SCD patient experienced with MBI co-runs each session with instructor supervision).

Lastly, specific and non-specific moderators and mediators of MBI effects on pain should be investigated. A new theoretical framework of mindfulness-based pain management (Day et al., 2014) proposes a number of testable moderators and mediators to explain MBIs potential effectiveness. The moderators and mediators described in this

framework have not been tested. In addition to the variables listed in their framework, additional mediators and moderators of interest for MBIs in SCD would be perceived stigma (disease stigma, race stigma, drug-seeking stigma), chronic pain duration (measured in years), socioeconomic status, social support, number of comorbid pain conditions, hydroxyurea prescription, and number and type of pain medications.

**Table 25 - Recommendations Summary**

	<b>What was done</b>	<b>Recommended Change</b>
<b>Recruitment</b>	In-person, brief screen for eligibility	Motivational Interviewing – more in-depth screening of potential participants
<b>Randomization procedures</b>	Randomized all enrolled patients before collecting baseline assessments	Randomize only participants that have returned baseline assessment
<b>MBI Design</b>	6 session, once a week for 60 minutes	6 session – once a week for 60 minutes; Potential modifications: <ul style="list-style-type: none"> <li>- Tailored design (individual vs. group)</li> <li>- Patient co-run</li> <li>- Relapse prevention strategies</li> </ul>
<b>Control Design</b>	Wait-listed control	Active control condition (sham mindfulness) or other active treatment condition (e.g., CBT, ACT)
<b>Questionnaires</b>	PCS, BPI, MAAS, PROMIS, PHQ9	Non-specific mediators: perceived stigma (disease stigma, race stigma, drug-seeking stigma), chronic pain duration (measured in years), socioeconomic status, number of comorbid pain conditions, hydroxyurea prescription, and number and type of pain medications.
<b>Assessment Frequency</b>	Baseline, Week 1, 3, 6	Baseline, Week 1 through 6; post-intervention follow-up at 3 & 6 months
PCS = Pain Catastrophizing Scale; PROMIS = Patient Report Outcomes Measurement Information System; MAAS = Mindful Awareness Attention Scale; BPI = Brief Pain Inventory; PHQ = Patient Health Questionnaire 9-item;		

## **4.8 Conclusion**

This pilot study represents an initial attempt to administer a telephonic MBI to persons with SCD and chronic pain. Our results support the feasibility and acceptability

of this telephonic MBI delivered to persons with SCD and chronic pain, and provides preliminary support demonstrating a moderate to strong MBI intervention effect on pain catastrophizing. Additional work is needed to explore MBI effects on pain and pain-related outcomes for persons with SCD and chronic pain.

## **5. Chapter 5: Conclusion**

### ***5.1 Summary***

Persons with SCD experience a variety of acute and chronic complications, but arguably one of the most difficult complications to manage is chronic pain. It is estimated that in SCD 55% of persons experience chronic pain (Smith et al., 2008) and 78% use long or short-acting opioids to manage their pain (Smith et al., 2015). And coinciding with chronic pain in SCD is pain catastrophizing (e.g., pain-related rumination, helplessness, magnification), which is associated with increased pain intensity, pain behavior, analgesic consumption, frequency and duration of hospital visits, and with reduced daily activities (Sullivan, Bishop, & Pivik, 1995; Keefe et al., 2000; Jacobsen & Butler, 1996; Bedard et al., 1997; Gil et al., 1992; Gil et al., 1993; Keefe et al., 1989). Thus there is a great need for non-pharmacological interventions for persons with SCD to help manage chronic pain, pain catastrophizing, and other pain-related complications, yet at this time there is scarce evidence to support or deny the efficacy of almost any non-pharmacological intervention for pain in SCD.

Recent statements made by multiple U.S. government organizations support this claim. The Center for Disease Control (CDC) in 2016 published a updated opioid prescription guidelines, and in this report state that non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain, and that if opioid therapy is prescribed, it should be combined with a non-pharmacological approach (MMWR, 2016). Additionally, the report also emphasizes the high comorbidity of depression and anxiety

that coincides with chronic pain, and that clinicians should ensure treatment of depression and anxiety along with other mental health conditions to optimize chronic pain management (MMWR, 2016). And a second report, the National Pain Strategy, published by the National Institute of Health – Interagency Pain Research Coordinating Committee in 2016 emphasizes that new “integrated, multimodal, and interdisciplinary treatments” need to be developed for chronic pain, as well as improvements to access of high-quality pain services for vulnerable population groups, such as those with SCD (IPRRC, 2016). Lastly, the 2014 treatment guidelines for SCD published by the National Heart Lung and Blood Institute (NHLBI, 2014) state that adding non-pharmacological approaches ‘may’ enhance management of chronic pain in SCD, but that the quality of available evidence to support the use of non-pharmacological treatments for persons with SCD is currently very low. Therefore it is difficult to overstate the importance and future development of non-pharmacological interventions for chronic pain management in persons with SCD.

## ***5.2 Literature Review (Chapter 2)***

A systematic review of the literature was conducted to describe and synthesize the use of non-pharmacological interventions for persons with SCD. The review found 28 studies that tested a non-pharmacological intervention designed to affect change in the intensity, duration, or frequency of pain in persons with SCD. A variety of non-pharmacological interventions were tested, which included skilled-based therapies ( $n = 23$ ; e.g., cognitive behavioral therapy, biofeedback, hypnosis, massage, acceptance and commitment therapy, aquatic rehabilitation) and peer-support groups ( $n = 5$ ). Of the 28

studies, 12 yielded significant improvements in pain (average effect size of .332 across measurable studies), three studies reported no positive effect or differences between experimental and control conditions on pain, and one reported a negative or detrimental intervention effect. The one study that reported a negative intervention effect was with cognitive-behavioral therapy, which found cognitive-behavioral therapy increased the number of pain episodes compared to hydroxyurea (Cummins, 2003). It was concluded that cognitive-behavioral therapy is the only non-pharmacological intervention with strong evidence (multiple randomized controlled trials) supporting its efficacy for persons with SCD and chronic pain (Williams & Tanabe, 2016).

### ***5.3 Healthcare Utilization (Chapter 3)***

With an extremely high percentage of persons with SCD reporting chronic pain, coupled with a lack of evidence for the use of non-pharmacological interventions for pain management, it is not surprising that many persons with SCD have frequent hospital admissions, and ED and day hospital visits. Between 1997 and 2007 there were approximately 1.6 million visits (197,000 p/year) by persons with SCD (Yusuf, Atrash, Grosse, Parker, Grant, 2010), and in 2010 the highest 30-day readmission rate of any acute and chronic condition was SCD (31.9% of all readmissions), accounting for approximately 87,326 hospital admissions and 27,837 readmissions (Elixhauser & Steiner, 2013). A number of medical factors have been associated with utilization of healthcare services by persons with SCD (Sobota et al., 2012; Ballas & Lusardi, 2005), but far less is known about what behavioral or social factors are associated with

healthcare utilization. To better understand what behavioral and social factors may be associated with higher utilization of healthcare services, a prospective correlational study was conducted with 95 patients with SCD that received care at one of two hospitals in North Carolina for a VOC.

In the study, patients participated in an interview within 14 days of an acute care encounter to evaluate behavioral factors (depression, anxiety, illicit drug use) and social factors (unemployment, unstable housing) potentially associated with high healthcare utilization. Information related to frequency of healthcare visits (hospital admissions, ED visits, day hospital visits) was obtained by a report of all ICD-9 codes associated with a VOC (282.6, 282.60-64, 282.68-69) for each of the 95 unique patients across the time period of the study. We found a high prevalence of depression (29%), anxiety (34%), unstable home environment (17%), unemployment (81%), and low illicit drug use (6%). After controlling for site differences, the only behavioral or social factor associated with increased frequency of healthcare utilization was unemployment. To the best of our knowledge, no other studies have tested or reported on social factors and healthcare utilization in persons with SCD seeking treatment for a VOC pain. When placed in context within the SCD literature, the findings from this study highlight that in addition to physical and behavioral factors, social factors are also important and should be taken into consideration when managing the care of a person with SCD.

#### ***5.4 Mindfulness-based Intervention (Chapter 4)***

To improve the management of chronic pain and overall quality of life for persons with SCD, an intervention is needed that is easily accessible to someone with debilitating chronic pain, and appropriate for persons that have frequent hospital admissions and ED visits, and report anxiety, depression, and overall negative affect. A promising category of non-pharmacological interventions for persons with SCD are Mindfulness-Based Interventions (MBIs) (Thompson, Walker, Obolensky, Winning, Barmon, et al., 2010; Cox, Porter, Buck, Hoffa, et al., 2013). The first MBI study that demonstrated efficacy in reducing chronic pain and improving pain coping (33% reduction in mean total of a pain rating index) was with a diverse group of chronic pain patients 30 years ago (Kabat-Zinn, 1984). Since that first publication multiple systematic and Cochrane reviews on the utility of MBIs for pain and pain coping have been published (Veehof et al., 2011). Perhaps one of the most important MBI findings for persons with SCD is the potentially long lasting effects. Sustained benefits of improved coping, decreased somatic complaints and depression, improved quality of life, and reduced pain intensity have been found up to three years after MBI program completion for some chronic pain patients (Grossman et al., 2007). Thus, persons with SCD and chronic pain who experience related physical and/or behavioral symptoms may experience long-term benefits by participating in a MBI program. However, no MBI studies have been conducted on persons with SCD; it is unknown if the generalizability of MBI's positive results will translate for persons with SCD and chronic pain.

A single site, randomized controlled pilot study was therefore conducted to test the feasibility, acceptability, and efficacy of a telephonic, group-based MBI for persons with chronic pain and SCD. Sixty persons with SCD were recruited at the Duke University Comprehensive Adult Sickle Cell Center, and randomized to either a MBI condition or control condition. Acceptability and feasibility were determined by assessment of recruitment, attrition, dropout, and refusal rates (including refusal reasons), along with semi-structured interviews that were conducted with 10 randomly selected patients at the end of study. Secondary outcome measurements (PCS, BPI, MAAS, PHQ-9, PROMIS) were collected at four time points: baseline, end of Session (Week) 1, 3, and 6.

We found that the telephonic MBI is feasible and acceptable for persons with SCD and chronic pain. Seventy-eight patients with SCD and chronic pain were approached, and 76% (N = 60) were enrolled and randomized. The MBI attendance rate, approximately 57% of participants completing at least four mindfulness sessions, was deemed acceptable, and participants that received the telephonic MBI described it as acceptable, easy to access, and consume in post-intervention interviews. The amount of missing data was undesirable (MBI condition, 40%; control condition, 25%), but fell within the range of expected missing outcome data for a RCT conducted within a clinical. Unfortunately efficacy of the MBI on pain catastrophizing could not be determined due to small sample size and degree of missing data, but trajectory analyses conducted for the MBI condition only trended in the right direction and two of the subscales (PCS –

Magnification; PROMIS – mental) approached statistical significance. Replication of this MBI study with a larger sample size, active control group, and additional assessments at the end of each week (e.g., Week 1 through Week 6) is needed to determine treatment efficacy.

## ***5.5 Future Directions***

### **5.5.1 Implications for Clinical Practice**

Care of persons with SCD requires a multi-disciplinary team of healthcare professionals that include physicians, nurses, nurse practitioners, physician assistant's social workers, and psychologists. Each of these healthcare providers has a unique opportunity to screen and refer patients that experience chronic pain to specially trained MBI clinicians, or integrative-medicine centers for non-pharmacological interventions. Despite the potential positive effect of a MBI, there are numerous barriers that limit a provider's ability to make referrals. Common barriers from the providers perspective include lack of reimbursement by insurance companies (e.g., not covering complementary and alternative treatments, restricted number of hours for CBT), lack of financial motivation (e.g., no pay-for-performance clinician incentive), and for some, deficiency in education and awareness of potential benefits of non-pharmacological interventions (IPRRC, 2016). To overcome these barriers systemic changes are needed within the healthcare system, specifically with how healthcare is delivered to make non-pharmacological interventions more readily accessible and easier for patients to receive.

### **5.5.2 Implications for Future Research**

As stated by the NHLBI guidelines on SCD management, “the quality of available evidence to support the use of non-pharmacological treatments for persons with SCD is currently very low” (NHLBI, 2014). Moving forward, multisite randomized controlled studies are needed to further test for efficacy of MBI interventions for chronic pain management in persons with SCD. Ideally these randomized controlled trials would compare between different types of non-pharmacological treatments (e.g., CBT vs MBSR vs ACT vs rTMS vs ECT vs MBSR+rTMS vs ECT+CBT etc.). A list of additional recommendations for future MBI studies can be found in Table 25.

In addition to randomized controlled trials, it is unknown how non-pharmacological interventions, like MBIs, reduce pain. There is limited evidence to support any mechanism through which pain reduction is achieved by a MBI. One study found that mindfulness meditation is not mediated by endogenous opioids (Zeidan et al., 2016), while another study found that it is mediated by endogenous opioids (Sharon et al., 2016). Other studies have shown neurophysiological changes associated with mindfulness meditation, sometimes in areas of the brain with high concentrations of opioid receptors, and other parts of the brain without high concentrations of opioid receptors (Zeidan et al., 2010, 2011, 2012, 2015). Future exploration of MBI mechanisms for pain should include active-control sham mindfulness conditions. A sham-mindfulness condition makes a participant believe they are performing ‘mindfulness meditation’, but in reality they are not because they are not instructed to be in the present moment, or

accepting (non-judgmental awareness) of thoughts, feelings, or sensations (Zeidan et al., 2015).

Non-specific moderators and mediators of MBI effects on pain have not been thoroughly investigated. A new theoretical framework of mindfulness-based pain management (Day et al., 2014) proposes a number of testable moderators and mediators to explain MBIs potential effectiveness. These moderators and mediators have not yet been tested. In addition to the variables listed in their framework, additional mediators and moderators of interest for a MBI in SCD would be stigma (disease stigma, race stigma, drug-seeking stigma), chronic pain duration (measured in years), socioeconomic status, number of comorbid pain conditions, hydroxyurea prescription, and number and type of pain medications.

## ***5.6 Conclusion***

In conclusion it is vital that additional research, specifically high-quality randomized controlled trials be conducted in the area of non-pharmacological interventions for persons with SCD and chronic pain. A telephonic MBI was found to be both feasibility and acceptable to persons with SCD and chronic pain, but the efficacy of the MBI on pain catastrophizing and other pain-related outcomes could not be determined. So as we quickly move forward with the integration of non-pharmacological approaches for chronic pain (CDC, 2006), it is crucial that we continue to research and explore for whom these approaches work best for, under what conditions, and potential

side effects before we make non-pharmacological approaches one of the primary forms of treatment for persons with SCD and chronic pain.

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## **Biography**

Hants Williams was born in Redwood City, California on January 14<sup>th</sup> 1987. He is a first generation American, and was raised in the Bay Area by his father (Andy) and mother (Lesley). He attended Junipero Serra High School and Carlmont High School, and graduated from San Jose State University with a double major in Behavioral Science and Psychology, and from San Francisco State University with a B.S.N. He is currently a Ph.D. candidate at Duke University School of Nursing. In 2013, Hants was the recipient of a Pre-doctoral Individual National Research Service Award from the National Institutes of Health, National Institute of Nursing Research. Beginning Summer 2016, he will begin a post-doctoral fellowship in the Department of Pain and Transitional Symptom Science at the University of Maryland School of Nursing, where he will continue focusing on the development and testing of non-pharmacological approaches for chronic pain.