A Multidimensional Understanding of Pain Among Adolescents and Adults with Sickle Cell Disease: A Prospective, Predictive, Correlational Study

by

Clare M. Kuisell

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in the University of Michigan
2020

Doctoral Committee:

Professor Ellen Lavoie Smith, Chair
Professor Raymond J. Hutchinson
Research Professor Robert J. Ploutz-Snyder
Associate Professor Terri Voepel-Lewis
Professor David A. Williams

Clare M. Kuisell

claremd@umich.edu

ORCID iD: 0000-0003-4387-4413

DEDICATION

This dissertation is dedicated to my husband, Ben, for his constant love and support throughout my doctoral studies. I would like to also dedicate this dissertation to my parents; without them, none of this would have been possible. Lastly, I thank God for giving me this incredible opportunity to broaden my understanding of symptom management, patient advocacy, and holistic nursing care.

ACKNOWLEDGEMENTS

I would like to acknowledge the clinical teams within the Adult and Pediatric Comprehensive Sickle Cell Clinics at Michigan Medicine and Mott Children's Hospital. Albert Query, MD, and Sharon Singh, MD, were instrumental in facilitating the implementation of study procedures and identifying patients in the clinics. In addition, I would like to acknowledge Brianna Finley for her assistance with recruitment and data collection. I would like to acknowledge Eric Maslowski and the staff at MoxyTech, Inc., for their assistance with the GeoPain @ Home application features and data management.

Funding for this study was provided by the Hillman Advancing Early Research Opportunities Grant, Rackham Graduate Student Research Grant, and the University of Michigan School of Nursing New Investigator Award.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABSTRACT

Sickle Cell Disease (SCD) is a disorder that disrupts the lives of thousands of Americans and causes recurring pain. Multidimensional factors including centralized pain, pain catastrophizing, and centrally-mediated symptoms, or the S.P.A.C.E. symptom cluster (i.e., sleep impairment, widespread pain, depression, anxiety, cognitive function, and fatigue) influence pain perception. Having comprehensive knowledge of the SCD-associated pain characteristics could lead to more effective pain management approaches. However, little SCD research has evaluated the incidence and severity of these multidimensional factors.

The purpose of this longitudinal study was to: 1) describe the incidence and severity of several pain influencing factors including pain catastrophizing, centralized pain, and S.P.A.C.E. symptoms (sleep impairment, multifocal pain, depression, anxiety, cognitive function, fatigue) in adolescents and young adults with SCD, 2) evaluate the predictive relationships among S.P.A.C.E. symptoms, opioid consumption, and pain interference, 3) examine the predictive relationships among pain catastrophizing, centralized pain, opioid consumption, and pain interference, and 4) characterize the co-occurrence of baseline S.P.A.C.E. symptoms, pain interference, opioid consumption, pain intensity, and Pain Area and Intensity Number Summation [P.A.I.N.S. (a metric that combines pain intensity and widespread pain)].

Forty-eight adolescents and adults with SCD were recruited from Pediatric and Adult Sickle Cell Clinics. Participants completed baseline measures of pain catastrophizing, centralized pain, S.P.A.C.E. symptoms, pain intensity, and P.A.I.N.S. After the completion of baseline measures, participants completed weekly opioid consumption and pain interference surveys.

Two-part models were used to analyze the predictive relationships among the multidimensional factors, weekly pain interference, and average daily opioid consumption. Multiple Spearman correlations were calculated to characterize the co-occurrence of baseline S.P.A.C.E. symptom severity scores, pain interference, average daily opioid consumption, pain intensity, and P.A.I.N.S.

Baseline depression, anxiety, and pain catastrophizing severity were low. One-fourth of participants were positive for centralized pain. Widespread pain (β=0.16; $p < 0.05$) and centralized pain (β=0.13; $p < 0.05$) were the only factors that significantly predicted increased opioid consumption. Pain catastrophizing had a significant negative relationship with opioid consumption (β=-0.03; $p < 0.05$). Within the pain interference models, fatigue (β=0.04; $p < 0.05$) and centralized pain (β=0.06; $p < 0.05$) were the only factors that significantly predicted more pain interference over time. Many S.P.A.C.E. symptoms (i.e., sleep impairment, anxiety, depression, cognitive function, and fatigue) were moderately and significantly correlated with one another. Pain interference was moderately and significantly correlated with all but one S.P.A.C.E. symptom (depression). Widespread pain was the only S.P.A.C.E. symptom that was significantly associated with average daily opioid consumption, pain intensity, and P.A.I.N.S.

Our findings demonstrate significant predictive relationships between centralized pain, opioid consumption, and pain. The results of this study should be interpreted with caution due to suboptimal data completion rates, small sample size, and low symptom severity. Routine assessment of centralized pain may facilitate the implementation of individualized pain management approaches, which may subsequently reduce pain and opioid use and improve function and quality of life among patients with SCD.

CHAPTER I

Introduction

Sickle Cell Disease (SCD) is the most commonly inherited red blood cell disease in the United States (Norman & Miller, 2011; Vacca Jr & Blank, 2017). One in 375 African Americans and those of Middle Eastern Heritage have SCD (Norman & Miller, 2011; Vacca Jr & Blank, 2017). Those with SCD have genetic mutations resulting in misshapen red blood cells that easily adhere to each other and cause vaso-occlusion (Vacca Jr & Blank, 2017). Several complications arise from vaso-occlusion including organ damage, cardiovascular and pulmonary complications, and pain (Smith & Scherer, 2010).

Statement of the Problem

Pain is known as the hallmark of SCD (Platt et al., 1991; Vacca Jr & Blank, 2017). Several negative outcomes including frequent health service utilization, reduced function, poor quality of life, anxiety, and depression are associated with SCD-related pain (Adam et al., 2017; Benton, Ifeagwu, & Smith-Whitley, 2007; Jerrell, Tripathi, & McIntyre, 2011; Smith, Penberthy, Bovbjerg, Mcclish, & Roberts, 2008). Although pain and opioid use is substantial among patients with SCD, there are few effective pharmacologic and non-pharmacologic treatments that reduce the incidence and severity of pain within this population. Considering the multidimensional and individualized presentation of pain among patients with SCD may uncover effective pharmacologic and non-pharmacologic pain management approaches. Thus, research that evaluates the multidimensional pain characteristics, and explores the predictive relationships between these characteristics, pain, and opioid consumption is needed.

Purpose

The purpose of this research study is to evaluate the multidimensional impact of pain among adolescents and adults with SCD, including the incidence and severity of pain catastrophizing, centralized pain, and centrally-mediated S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, depression, anxiety, cognitive function, and fatigue). Further, the predictive relationships among these characteristics and average daily opioid consumption and weekly pain interference will be explored. This research will also characterize the co-occurrence of S.P.A.C.E. symptoms, average daily opioid consumption, pain interference, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) (Davis, Kroenke, Monahan, Kean, & Stump, 2017; Knoerl, Chornoby, & Smith, 2018; Williams, 2018).

Theoretical Approach

The Theory of Unpleasant Symptoms (TOUS) is the theoretical framework (Figure 1) that guides this dissertation study (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). According to this theory, physiologic, psychologic, and situational factors are all influencing factors that interact with each other in relation to the symptom (Lenz et al., 1997). Informed by empirical centralized pain literature, this study will examine the relationships among SCD pain-related factors within each theoretical construct based on an adapted TOUS framework (Figure 2). Below is a brief description of the variables included within the adapted TOUS framework.

Figure 1. ***The Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997)***

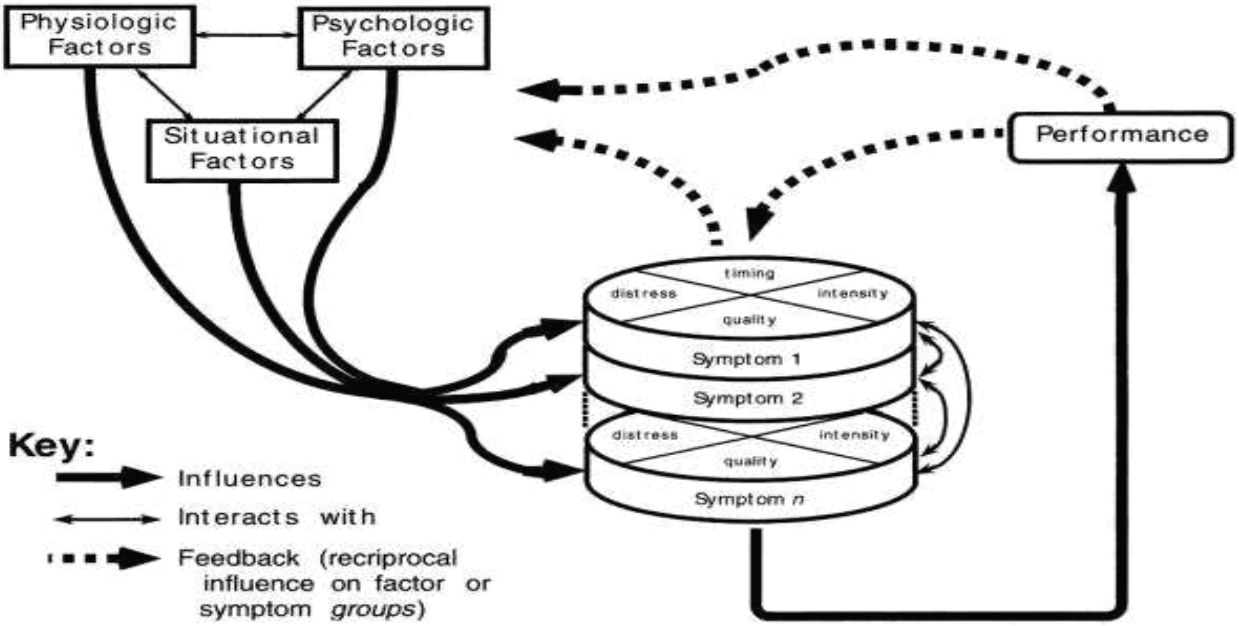
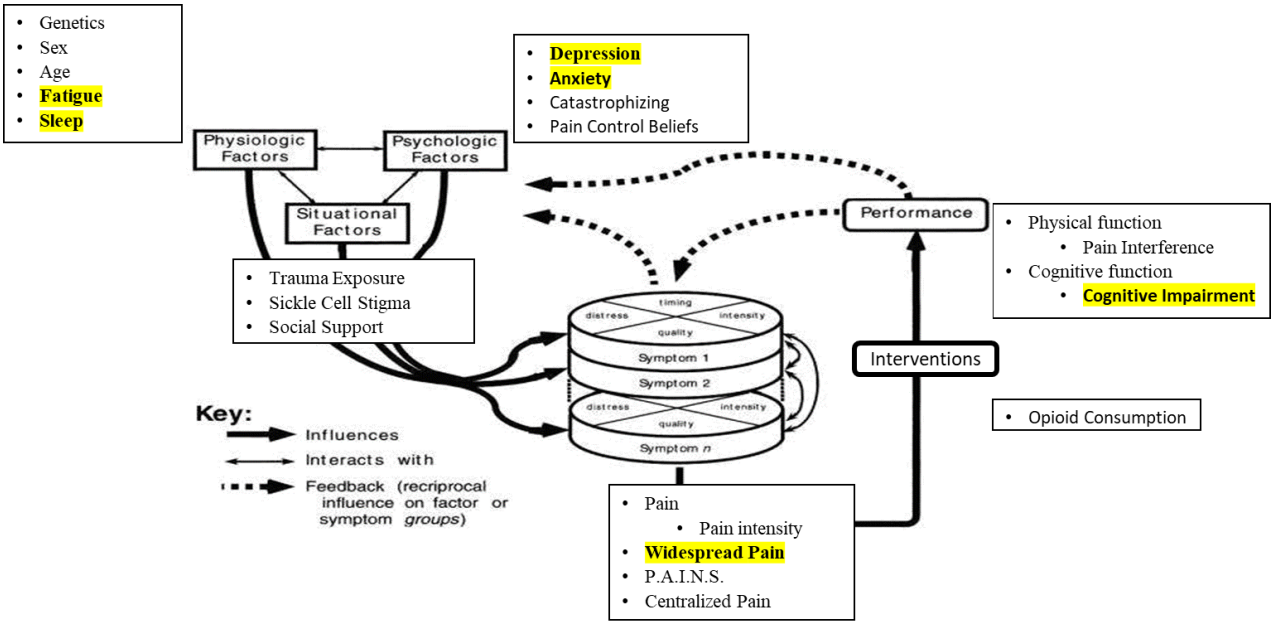


Figure 2. ***Adapted Theory of Unpleasant Symptoms***



Note. Highlighted text indicates S.P.A.C.E. symptoms; P.A.I.N.S.= Pain Area and Intensity Number Summation

Model Components

Physiologic factors.

The physiologic characteristics included within the adapted theoretical framework are genetics, age, sex, sleep, and fatigue. Empirical evidence suggests that genetic factors can influence pain sensitivity, analgesic response, and the development of centralized pain syndromes (i.e., fibromyalgia, temporomandibular disorders, and migraine)(Andersen & Skorpen, 2009; Diatchenko et al., 2005; Emin Erdal, Herken, Yilmaz, & Bayazit, 2001; Gursoy et al., 2003; Smith et al., 2012). One genetic factor unique to SCD is sickle cell genotype including HbSS, HbSC, HbS β^0, HbS β^+. However, there is conflicting evidence regarding pain differences among the different sickle cell genotypes (Carroll et al., 2016; Carroll, Haywood, Hoot, & Lanzkron, 2013; Jacob et al., 2015; McClish et al., 2009; Schlenz, Schatz, & Roberts, 2016; Sil, Cohen, & Dampier, 2016; Zempsky et al., 2017). The second physiologic factor included within the adapted theoretical model is sex. Empirical evidence suggests that females have increased pain frequency, sensitivity, and durations compared to males (Bartley & Fillingim, 2013; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Smith et al., 2006). Similarly to sickle cell genotype, there remains conflicting evidence regarding sex differences and pain among patients with SCD (Antunes, Propheta, Vasconcelos, & Cipolotti, 2017; Bakshi, Lukombo, Belfer, & Krishnamurti, 2018; Bakshi, Lukombo, Shnol, Belfer, & Krishnamurti, 2017; Brandow et al., 2013; Carroll et al., 2016; Graves & Jacob, 2014; Jacob et al., 2015; McClish et al., 2009; Sil et al., 2016; Zempsky et al., 2017).

Two additional physiologic variables, sleep and fatigue, are also included within the S.P.A.C.E. symptom cluster (Williams, 2018). Empirical evidence suggests that sleep impairment and pain are associated among patients with several centralized pain conditions, such

as chronic low back pain, temporomandibular disorders (TMD), and fibromyalgia (Choy, 2015; Heffner, France, Trost, Mei Ng, & Pigeon, 2011; Park & Chung, 2016). Further, research has highlighted associations between sleep impairment, pain frequency, pain severity, and SCD-related complications (Daniel, Grant, Kothare, Dampier, & Barakat, 2010; Moscou-Jackson, Finan, Campbell, Smyth, & Haythornthwaite, 2015; Wallen et al., 2014).

Lastly, fatigue, is a symptom commonly reported among patients with a variety of painful conditions (e.g., irritable bowel syndrome, migraine, TMD) (Dailey, Keffala, & Sluka, 2015; Lackner, Gudleski, Dimuro, Keefer, & Brenner, 2013; Lau, Lin, Chen, Wang, & Kao, 2015; Robinson, Durham, & Newton, 2016). Only one study, however, has investigated the relationship between fatigue and pain among patients with SCD (Ameringer, Elswick Jr, & Smith, 2014). It is hypothesized that increased sleep impairment and increased fatigue will predict increased weekly opioid consumption and pain interference among adolescents and young adults with SCD.

Psychologic factors.

The psychologic factors within the adapted model are depression, anxiety, catastrophizing, and pain control beliefs. Depression and anxiety are two variables that quantify affective perturbation within the S.P.A.C.E. symptom cluster (Davis et al., 2017; Knoerl et al., 2018; Williams, 2018). It is widely known that depression and pain co-occur in patients with centralized pain (Davis et al., 2017; Maletic & Raison, 2009; Strigo, Simmons, Matthews, Craig, & Paulus, 2008). Further, empirical evidence suggests that 35-46% of patients with SCD have depression (Adam et al., 2017; Jerrell et al., 2011). Studies conducted among patients with SCD also support a positive association between depression and pain frequency, multifocal pain, lower heat pain thresholds, opioid use, and SCD-related complications (Bakshi, Lukombo,

Shnol, Belfer, & Krishnamurti, 2017; Carroll et al., 2016b; Jerrell et al., 2011; McClish et al., 2009; S Sil, Dampier, & Cohen, 2016; Wallen et al., 2014). Thus, it is hypothesized that increased depression will predict increased weekly opioid consumption and pain interference among adolescents and young adults with SCD.

Anxiety is the second psychologic factor included within the adapted theoretical model. Empirical evidence suggests that anxiety is strongly associated with several pain conditions such as chronic low back pain, migraine, and arthritis (Davis et al., 2017; McWilliams, Cox, & Enns, 2003; McWilliams, Goodwin, & Cox, 2004; Tsang et al., 2008). There is conflicting evidence, however, regarding the association between anxiety and pain among patients with SCD. (Bakshi et al., 2018, 2017; Ford, Grasso, Jones, Works, & Andemariam, 2017; Jacob et al., 2015; Lemanek, Ranalli, & Lukens, 2009; Moody et al., 2017; Thomas, Stephenson, Swanson, Jesse, & Brown, 2013). Pain catastrophizing, an additional psychological factor, is conceptualized as irrational thoughts about pain including rumination, magnification and helplessness (Citero et al., 2007; Quartana & Edwards, 2009). Several studies support the association between catastrophizing and pain in patients with various pain conditions and those with SCD (Bakshi et al., 2017; Campbell et al., 2016; Ciechanowski, Sullivan, Jensen, Romano, & Summers, 2003; Finan et al., 2018; Geisser, Robinson, Keefe, & Weiner, 1994; Graves & Jacob, 2014; Keefe et al., 2000; Pavlin, Sullivan, Freund, & Roesen, 2005; Quartana & Edwards, 2009; Severeijns, Vlaeyen, van den Hout, & Weber, 2001; Sil, Cohen, et al., 2016). Based on the research described above, it is hypothesized that increased anxiety and pain catastrophizing will predict increased opioid consumption and pain interference among adolescents and young adults with SCD.

Pain control beliefs, or beliefs that pain is either controllable or uncontrollable, is the last psychologic factor included within the adapted theoretical model. Empirical evidence suggests that pain control beliefs influence how a patient processes and manages their pain (Higgins, Bailey, LaChapelle, Harman, & Hadjistavropoulos, 2015; Oliveira et al., 2009; Spinhoven et al., 2004). Limited evidence has investigated the relationship between pain control beliefs and pain in patients with SCD.

Situational factors.

The situational factors within the model are sickle cell stigma, trauma exposure, and social support. Sickle cell stigma is a factor unique to those with SCD. Evidence suggests that many clinicians who manage patients with SCD have misperceptions regarding rates of opioid misuse and addiction (Wakefield et al., 2017; Zempsky, 2009). Due to clinician bias and false assumptions about a patient's motivation for seeking pain medication, patients suffering with VOC-associated pain may not receive adequate treatment for their pain. Two studies have highlighted that perceived sickle cell stigma among patients is associated with increased pain interference and health care utilization (Bediako et al., 2016; Martin et al., 2018).

The second situational factor included within the adapted TOUS theoretical model is trauma exposure. Pain research in other centralized pain populations (e.g., irritable bowel syndrome, fibromyalgia, chronic back pain, chronic daily headaches, and chronic pelvic pain) suggests a significant positive relationship between trauma exposure (i.e., abuse, illness, parental upheaval, death of a family member or friend) and the development centralized pain disorders (Hauser, Kosseva, Uceyler, Klose, & Sommer, 2011; Kanzawa-Lee et al., 2018; Oram et al., 2012; Phillips & Clauw, 2011; Schofferman, Anderson, Hines, Smith, & Keane, 1993; Spiegel et

al., 2015). Few studies have explored the relationship between trauma exposure and pain among patients with SCD.

Lastly, empirical evidence suggests an association between pain and social support in centralized pain populations (Forgeron et al., 2010; Snelling, 1994; Zaza & Baine, 2002). Research has highlighted that the presence of a centralized pain condition may negatively impact a patient's social support network (Carter, Lambrenos, & Thursfield, 2002; Zaza & Baine, 2002). Conversely, patients with more social support are more likely to engage in positive coping strategies (Holtzman, Newth, & Delongis, 2004). Limited research has evaluated the association between pain and social support among patients with SCD (Carroll et al., 2013).

Symptoms.

Pain, widespread pain, and centralized pain are the symptoms included within the theoretical model. Widespread pain, or multifocal pain, is also included within the S.P.A.C.E. symptom cluster (Williams, 2018). Widespread pain is frequently reported among patients with centralized pain conditions such as fibromyalgia, temporomandibular disorder, and urologic chronic pelvic pain syndrome (Lai et al., 2017; Slade et al., 2013; Williams, 2018). Further, empirical evidence suggests that more than 20% of patients with SCD report pain in more than seven body sites (Zempsky et al., 2017). Based on this evidence, it is hypothesized that patients with widespread pain will have increased weekly opioid consumption and pain interference.

Pain intensity, a characteristic used to operationalize the symptom of pain, is included within the adapted theoretical model. Pain intensity is frequently assessed within clinical and research settings to inform pain management approaches and measure effectiveness. Limited research, however, has investigated the co-occurrence of pain intensity with multiple centrally-mediated symptoms among patients with SCD. For this reason, we seek to understand the co-

occurrence of centrally-mediated symptoms and pain intensity. Since pain intensity does not capture the multidimensional aspect of pain, we will also evaluate Pain Area and Intensity Number Summation (P.A.I.N.S.). P.A.I.N.S. is a single variable that combines pain intensity and widespread pain and provides a more comprehensive evaluation of the painful experience.

The third symptom included within the adapted TOUS model is centralized pain. Centralized pain arises from altered nociception in the absence of actual or potential tissue damage or evidence for disease or lesion of the somatosensory system (Latremoliere & Woolf, 2009; Marchand, 2008; Woolf, 2011). A growing body of literature suggests that a subset of patients with SCD experience centralized pain (Brandow, Stucky, Hillery, Hoffmann, & Panepinto, 2013; Campbell et al., 2016; Carroll et al., 2016; Jacob et al., 2015). Research conducted in other centralized pain populations suggests that opioids are ineffective for centralized pain (Brummett et al., 2013; Corli et al., 2017; Finan et al., 2018; Hanks & Forbes, 1997; Janda et al., 2015; Phillips & Clauw, 2011; Wasserman, Brummett, Goesling, Tsodikov, & Hassett, 2014). This suboptimal pain relief may be manifested by increased daily pain and increased daily opioid consumption. Based on this evidence, it is hypothesized that patients with SCD experiencing centralized pain will have increased opioid consumption and pain interference.

Interventions.

Opioid consumption is conceptualized as an intervention within the adapted TOUS model. An acute (short-lived) pain episode, also called a vaso-occlusive pain crisis (VOC), is the most common complication of SCD (Vacca Jr & Blank, 2017). For this reason, many of the treatments available for SCD-related pain focus on managing acute pain episodes. Clinical practice guidelines published by the National Heart Lung and Blood Institute (2014) support the

rapid initiation of analgesics, opioids and non-opioids, when patients present with VOC. Further, in those that present with severe pain, the initiation of parenteral opioids is strongly recommended (National Heart, Lung, and Blood Institute, 2014). Although opioids are indicated for acute VOC, evidence suggests that they are ineffective in treating the variety of pathophysiologic mechanisms that contribute to centralized pain (Brummett et al., 2013; Corli et al., 2017; Finan et al., 2018; Hanks & Forbes, 1997; Janda et al., 2015; Phillips & Clauw, 2011; Wasserman, Brummett, Goesling, Tsodikov, & Hassett, 2014). Despite this, daily opioid use in those with SCD remains substantial (Finan et al., 2018). To guide the implementation of effective non-opioid and non-pharmacologic interventions among patients with SCD, it is necessary to understand the pain presentation unique to those with SCD. For this reason, we will evaluate the predictive relationships among the various centrally-mediated symptoms, pain catastrophizing, centralized pain, and opioid consumption.

Performance.

The adapted model depicts that influencing factors and symptoms influence an individual's physical or cognitive performance (Lenz et al., 1997). Physical performance will be conceptualized within this study as pain interference, or the consequences of pain on relevant aspects of one's life (Amtmann et al., 2010). Pain interference has been chosen as a primary outcome within this study to provide information regarding the functional impact of pain among patients with SCD.

Cognitive performance is conceptualized as cognitive function and is the last variable included within the S.P.A.C.E. symptom cluster (Williams, 2018). Empirical evidence suggests that cognitive function and pain are correlated among patients with multiple sclerosis and fibromyalgia (Glass, 2009; Kratz, Murphy, & Braley, 2017; Shattuck & Muehlenbein, 2016; D.

A. Williams, 2018). However, no studies have examined the predictive relationship between cognitive function and pain among patients with SCD. Based on evidence within other pain populations, it is hypothesized that decreased cognitive function will predict increased opioid consumption and pain interference among adolescents and young adults with SCD (Heffner et al., 2011; Park & Chung, 2016; Schaible, 2014; Shattuck & Muehlenbein, 2016).

This chapter has provided a brief review of several physiological, psychological, situational, and cognitive factors that have been associated with pain among patients with SCD. These factors included genetics, sex, age, sleep, depression, anxiety, cognitive function, fatigue, catastrophizing, pain control beliefs, sickle cell stigma, trauma exposure, social support. Although several of the factors discussed require further investigation (e.g., sickle cell stigma, trauma exposure, pain control beliefs), their relationships with opioid consumption and pain interference will not be explored in the proposed study due to sample size limitations and participant burden. The factors that will be investigated within this study were selected based on significant gaps identified within the SCD literature. There is a paucity of research that has evaluated centralized pain and the severity, co-occurrence, and impact of all centrally-mediated symptoms within the S.P.A.C.E. symptom cluster (Davis et al., 2017; Robert Knoerl et al., 2018; Shattuck & Muehlenbein, 2016; D. A. Williams, 2018). Further, there is conflicting evidence regarding the predictive relationship between catastrophizing and pain among those with SCD. For these reasons, the factors that will be explored within this study include centralized pain, pain catastrophizing, centrally-mediated symptoms included within the S.P.A.C.E. symptom cluster, pain interference, and opioid consumption.

In summary, the adapted TOUS model has guided the inclusion of several variables within the proposed study and their hypothesized relationships. It is hypothesized that several

individual factors will predict weekly opioid consumption and pain interference one month after baseline phenotyping. Lastly, the co-occurrence of baseline S.P.A.C.E. symptoms, pain interference, average daily opioid consumption, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) will be evaluated via correlation coefficients within this population.

Specific Aims and Hypotheses

To achieve our overall objective, we will address the following specific aims:

SA1- Characterize demographic variables (i.e., age, sex, and sickle cell genotype), the incidence and severity of centralized pain, pain catastrophizing, and six S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, depression, cognitive function, fatigue) measured at baseline among adolescents and adults with SCD.

SA2- Evaluate the predictive relationships among demographic variables (i.e., age and sex), baseline S.P.A.C.E. symptoms (sleep impairment, widespread pain, anxiety, depression, cognitive function, fatigue) and opioid consumption and pain interference reported longitudinally for one month post-baseline in adolescents and young adults with SCD.

SA2a- Evaluate the predictive relationships among age, sex, S.P.A.C.E. symptoms, and average daily opioid consumption (milligram milliequivalents [MME]) measured by weekly opioid surveys.

SA2b- Evaluate the predictive relationships among age, sex, S.P.A.C.E. symptoms, and weekly pain interference measured by the Patient Reported Outcome Measures Information System (PROMIS®) Pain Interference measure.

Hypothesis- Baseline evidence of sleep impairment, widespread pain, anxiety, depression, cognitive impairment, and fatigue will predict increased opioid

consumption (MME) and pain interference one month post-baseline in adolescents and young adults with SCD.

SA3- Examine the predictive relationships among baseline centralized pain and pain catastrophizing severity, opioid consumption, and pain interference within one month of baseline phenotyping.

SA3a- Examine the predictive relationships of baseline centralized pain and pain catastrophizing severity, and average daily opioid consumption (MME) measured by weekly opioid consumption surveys.

SA3b- Examine the predictive relationships of baseline centralized pain and pain catastrophizing severity, and weekly pain interference measured by the PROMIS® Pain Interference measure.

Hypothesis- Baseline centralized pain severity and pain catastrophizing severity will predict increased opioid consumption (MME) and pain interference one month post-baseline in adolescents and young adults with SCD.

SA4- Characterize the co-occurrence of baseline S.P.A.C.E. symptoms, average daily opioid consumption, pain interference, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) measured via an interactive body map within the GeoPain @ Home mobile application.

Future Directions

The results of this study provide comprehensive information regarding the incidence and severity of several centrally-mediated symptoms and pain-related characteristics among adolescents and adults with SCD. Further, this research examined the predictive relationships among baseline characteristics and opioid consumption and pain interference. Lastly, the

findings of this study identified the co-occurrence of several centrally-mediated symptoms, opioid consumption, and pain among adolescents and young adults with SCD. Together, these findings suggest that centralized pain and many centrally-mediated symptoms factors predict opioid consumption and pain that interferes with social, emotional, and physical function. Assessment of centrally-mediated symptoms and centralized pain is necessary to improve individualized pain management among patients with SCD. Clinicians can use knowledge about the incidence and severity of centralized pain and centrally-mediated symptoms to facilitate referrals to clinical specialists (e.g., integrative health providers) and ancillary resources (e.g., psychiatric). Further, individualized evaluation and management of pain can inform the implementation of appropriate non-pharmacologic treatments. Ultimately, individualized pain management approaches, informed by centrally-mediated symptoms and pain-influencing factors, may reduce pain and opioid use and improve function and quality of life among patients with SCD.

Within the following chapters, I will describe the supporting literature, methods, results, and discussion that address each aim of this dissertation project. Chapter 2 includes an overview of pain definitions, incidence, characteristics, pathophysiology, and pain unique to patients with SCD. Chapter 3 addresses Aims 1 and 4, including a description of the incidence and severity of S.P.A.C.E. symptoms and their co-occurrence with opioid consumption and negative pain outcomes among adolescents and adults with SCD. The evaluation of the predictive relationships among centralized pain severity, pain catastrophizing severity, weekly opioid consumption and pain interference (Aim 3) is described in Chapter 4. Further, the evaluation of the predictive relationships among baseline S.P.A.C.E. symptoms and weekly opioid consumption and pain

interference (Aim 2) is described in Chapter 5. Lastly, Chapter 6 concludes this dissertation with a broad discussion of the results of this dissertation project and implications for future research.

References

Adam, S. S., Flahiff, C. M., Kamble, S., Telen, M. J., Reed, S. D., & De Castro, L. M. (2017). Depression, quality of life, and medical resource utilization in sickle cell disease. *Blood Advances*, *1*(23), 1983–1992. https://doi.org/10.1182/bloodadvances.2017006940 [doi]

Ameringer, S., Elswick Jr, R. K., & Smith, W. (2014). Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing*, *31*(1), 6–17. https://doi.org/10.1177/1043454213514632 [doi]

Amtmann, D., Cook, K. F., Jensen, M. P., Chen, W. H., Choi, S., Revicki, D., … Lai, J. S. (2010). Development of a PROMIS item bank to measure pain interference. *Pain*, *150*(1), 173–182. https://doi.org/10.1016/j.pain.2010.04.025 [doi]

Andersen, S., & Skorpen, F. (2009). Variation in the COMT gene: Implications for pain perception and pain treatment. *Pharmacogenomics*, *10*(4), 669–684. https://doi.org/10.2217/pgs.09.13

Antunes, F. D., Propheta, V. G. S., Vasconcelos, H. A., & Cipolotti, R. (2017). Neuropathic pain in patients with sickle cell disease: a cross-sectional study assessing teens and young adults. *Annals of Hematology*. https://doi.org/10.1007/s00277-017-2984-z

Bakshi, N., Lukombo, I., Belfer, I., & Krishnamurti, L. (2018). Pain catastrophizing is associated with poorer health-related quality of life in pediatric patients with sickle cell disease. *Journal of Pain Research*, 947–953.

Bakshi, N., Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anaesthesia*, *111*(1), 52–58. https://doi.org/10.1093/bja/aet127

Bediako, S. M., Lanzkron, S., Diener-West, M., Onojobi, G., Beach, M. C., & Haywood, C. (2016). The Measure of Sickle Cell Stigma: Initial findings from the Improving Patient Outcomes through Respect and Trust study. *Journal of Health Psychology*, *21*(5), 808–820. https://doi.org/10.1177/1359105314539530

Benton, T. D., Ifeagwu, J. A., & Smith-Whitley, K. (2007). Anxiety and depression in children and adolescents with sickle cell disease. *Current Psychiatry Reports*, *9*(2), 114–121.

Brandow, A. M., Stucky, C. L., Hillery, C. A., Hoffmann, R. G., & Panepinto, J. A. (2013). Patients with sickle cell disease have increased sensitivity to cold and heat. *American Journal of Hematology*. https://doi.org/10.1002/ajh.23341

Brummett, C. M., Janda, A. M., Schueller, C. M., Tsodikov, A., Morris, M., Williams, D. A., & Clauw, D. J. (2013). Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective,

observational cohort study. *Anesthesiology*, *119*(6), 1434–1443. https://doi.org/10.1097/ALN.0b013e3182a8eb1f [doi]

Campbell, C. M., Moscou-Jackson, G., Carroll, C. P., Kiley, K., Haywood, C., Lanzkron, S., … Haythornthwaite, J. A. (2016). An Evaluation of Central Sensitization in Patients With Sickle Cell Disease. *The Journal of Pain*, *17*(5), 617–627. https://doi.org/10.1016/j.jpain.2016.01.475

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, P. C., Haywood, C., Hoot, M. R., & Lanzkron, S. (2013). A preliminary study of psychiatric, familial, and medical characteristics of high-utilizing sickle cell disease patients. *Clinical Journal of Pain*, *29*(4), 317–323. https://doi.org/10.1097/AJP.0b013e3182579b87

Carter, B., Lambrenos, K., & Thursfield, J. (2002). A pain workshop: an approach to eliciting the views of young people with chronic pain. *Journal of Clinical Nursing*, *11*(6), 753–762.

Choy, E. H. S. (2015). The role of sleep in pain and fibromyalgia. *Nature Reviews. Rheumatology*, *11*(9), 513–520. https://doi.org/10.1038/nrrheum.2015.56

Ciechanowski, P., Sullivan, M., Jensen, M., Romano, J., & Summers, H. (2003). The relationship of attachment style to depression, catastrophizing and health care utilization in patients with chronic pain. *Pain*, *104*(3), 627–637.

Corli, O., Roberto, A., Bennett, M. I., Galli, F., Corsi, N., Rulli, E., & Antonione, R. (2017). Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Practice*. https://doi.org/10.1111/papr.12669 [doi]

Dailey, D. L., Keffala, V. J., & Sluka, K. A. (2015). Do cognitive and physical fatigue tasks enhance pain, cognitive fatigue, and physical fatigue in people with fibromyalgia? *Arthritis Care & Research*, *67*(2), 288–296. https://doi.org/10.1002/acr.22417

Daniel, L. C., Grant, M., Kothare, S. V, Dampier, C., & Barakat, L. P. (2010). Sleep Patterns in Pediatric Sickle Cell Disease. *Pediatr Blood Cancer*, (October 2009), 501–507. https://doi.org/10.1002/pbc

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2017). The SPADE Symptom Cluster in Primary Care Patients with Chronic Pain. *Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286.The

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., … Maixner, W. (2005). Genetic basis for individual variations in pain perception and the

development of a chronic pain condition. *Human Molecular Genetics*, *14*(1), 135–143. https://doi.org/10.1093/hmg/ddi013

Emin Erdal, M., Herken, H., Yilmaz, M., & Bayazit, Y. A. (2001). Significance of the catechol-O-methyltransferase gene polymorphism in migraine. *Brain Research. Molecular Brain Research*, *94*(1–2), 193–196.

Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley, J. L. (2009). Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *Journal of Pain*, *10*(5), 447–485. https://doi.org/10.1016/j.jpain.2008.12.001

Finan, P. H., Carroll, C. P., Moscou-Jackson, G., Martel, M. O., Campbell, C. M., Pressman, A., … Haythornthwaite, J. A. (2018). Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis. *The Journal of Pain*, *19*(1), 46–56. https://doi.org/10.1016/j.jpain.2017.08.010

Ford, J. D., Grasso, D. J., Jones, S., Works, T., & Andemariam, B. (2017). Interpersonal Violence Exposure and Chronic Pain in Adult Sickle Cell Patients. *Journal of Interpersonal Violence*, 886260517691521. https://doi.org/10.1177/0886260517691521

Forgeron, P. A., King, S., Stinson, J. N., McGrath, P. J., MacDonald, A. J., & Chambers, C. T. (2010). Social functioning and peer relationships in children and adolescents with chronic pain: A systematic review. *Pain Research and Management*, *15*(1), 27–41. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-77950464526&partnerID=40&md5=1b217295f888cc94f5cc4d05615801ae

Geisser, M. E., Robinson, M. E., Keefe, F. J., & Weiner, M. L. (1994). Catastrophizing, depression and the sensory, affective and evaluative aspects of chronic pain. *Pain*, *59*(1), 79–83.

Glass, J. M. (2009). Review of cognitive dysfunction in fibromyalgia: a convergence on working memory and attentional control impairments. *Rheumatic Diseases Clinics of North America*, *35*(2), 299–311. https://doi.org/10.1016/j.rdc.2009.06.002

Graves, J. K., & Jacob, E. (2014). Pain, coping, and sleep in children and adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing*, *27*(3), 109–120. https://doi.org/10.1111/jcap.12077 [doi]

Gursoy, S., Erdal, E., Herken, H., Madenci, E., Alasehirli, B., & Erdal, N. (2003). Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatology International*, *23*(3), 104–107. https://doi.org/10.1007/s00296-002-0260-5

Hanks, G. W., & Forbes, K. (1997). Opioid responsiveness. *Acta Anaesthesiologica Scandinavica*, *41*(1 Pt 2), 154–158.

Hauser, W., Kosseva, M., Uceyler, N., Klose, P., & Sommer, C. (2011). Emotional, physical, and sexual abuse in fibromyalgia syndrome: a systematic review with meta-analysis. *Arthritis Care & Research*, *63*(6), 808–820. https://doi.org/10.1002/acr.20328 [doi]

Heffner, K. L., France, C. R., Trost, Z., Mei Ng, H., & Pigeon, W. R. (2011). Chronic low back pain, sleep disturbance, and interleukin-6. *Clinical Journal of Pain*, *27*(1), 35–41. https://doi.org/10.1097/AJP.0b013e3181eef761

Higgins, N. C., Bailey, S. J., LaChapelle, D. L., Harman, K., & Hadjistavropoulos, T. (2015). Coping Styles, Pain Expressiveness, and Implicit Theories of Chronic Pain. *The Journal of Psychology*, *149*(7), 737–750. https://doi.org/10.1080/00223980.2014.977759

Holtzman, S., Newth, S., & Delongis, A. (2004). The role of social support in coping with daily pain among patients with rheumatoid arthritis. *Journal of Health Psychology*, *9*(5), 677–695. https://doi.org/10.1177/1359105304045381

Jacob, E, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*, *37*(3), 185–189. https://doi.org/10.1097/MPH.0000000000000214 [doi]

Jacob, Eufemia, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). *Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease*. *J Pediatr Hematol Oncol* (Vol. 37). Retrieved from www.jpho-online.com

Janda, A. M., As-Sanie, S., Rajala, B., Tsodikov, A., Moser, S. E., Clauw, D. J., & Brummett, C. M. (2015). Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology*, *122*(5), 1103–1111. https://doi.org/10.1097/ALN.0000000000000637 [doi]

Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary Care Companion for CNS Disorders*, *13*(2), 10.4088/PCC.10m01063. https://doi.org/10.4088/PCC.10m01063 [doi]

Kanzawa-Lee, G. A., Knoerl, R., Williams, D. A., Clauw, D. J., Bridges, C. M., Harte, S. E., … Lavoie Smith, E. M. (2018). Childhood Trauma Predicts Cancer Treatment-Related Pain in Breast Cancer Survivors. *Cancer Nursing*. https://doi.org/10.1097/NCC.0000000000000687

Keefe, F. J., Lefebvre, J. C., Egert, J. R., Affleck, G., Sullivan, M. J., & Caldwell, D. S. (2000). The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain*, *87*(3), 325–334.

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2018). Estimating the Frequency , Severity , and Clustering of SPADE Symptoms in Chronic Painful Chemotherapy- Induced Peripheral Neuropathy. *Pain Management Nursing*, *19*(4), 354–365. https://doi.org/10.1016/j.pmn.2018.01.001

Kratz, A. L., Murphy, S. L., & Braley, T. J. (2017). Pain, Fatigue, and Cognitive Symptoms Are Temporally Associated Within but Not Across Days in Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation*, *98*(11), 2151–2159. https://doi.org/10.1016/j.apmr.2017.07.003

Lackner, J. M., Gudleski, G. D., Dimuro, J., Keefer, L., & Brenner, D. M. (2013). Psychosocial predictors of self-reported fatigue in patients with moderate to severe irritable bowel syndrome. *Behaviour Research and Therapy*, *51*(6), 323–331. https://doi.org/10.1016/j.brat.2013.03.001

Lai, H. H., Jemielita, T., Sutcliffe, S., Bradley, C. S., Naliboff, B., Williams, D. A., … Landis, J.

R. (2017). Characterization of Whole Body Pain in Urological Chronic Pelvic Pain Syndrome at Baseline: A MAPP Research Network Study. *The Journal of Urology*, *198*(3), 622–631. https://doi.org/10.1016/j.juro.2017.03.132

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *Journal of Pain*, *10*(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012

Lau, C., Lin, C.-C., Chen, W.-H., Wang, H.-C., & Kao, C.-H. (2015). Increased risk of chronic fatigue syndrome in patients with migraine: A retrospective cohort study. *Journal of Psychosomatic Research*, *79*(6), 514–518. https://doi.org/10.1016/j.jpsychores.2015.10.005

Lemanek, K. L., Ranalli, M., & Lukens, C. (2009). A randomized controlled trial of massage therapy in children with sickle cell disease. *Journal of Pediatric Psychology*, *34*(10), 1091–1096. https://doi.org/10.1093/jpepsy/jsp015

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*, *19*(3), 14–27.

Maletic, V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Frontiers in Bioscience*, *14*, 5291–5338.

Marchand, S. (2008). The Physiology of Pain Mechanisms: From the Periphery to the Brain. *Rheumatic Disease Clinics of North America*, *34*(2), 285–309. https://doi.org/10.1016/j.rdc.2008.04.003

Martin, S. R., Cohen, L. L., Mougianis, I., Griffin, A., Sil, S., & Dampier, C. (2018). Stigma and Pain in Adolescents Hospitalized for Sickle Cell Vasoocclusive Pain Episodes. *The Clinical Journal of Pain*, *34*(5), 438–444. https://doi.org/10.1097/AJP.0000000000000553 [doi]

McClish, D. K., Smith, W. R., Dahman, B. A., Levenson, J. L., Roberts, J. D., Penberthy, L. T., … Bovbjerg, V. E. (2009). Pain site frequency and location in sickle cell disease: The PiSCES project. *Pain*, *145*(1–2), 246–251. https://doi.org/10.1016/j.pain.2009.06.029

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: An examination in a nationally representative sample. *Pain*, *106*(1–2), 127–133. https://doi.org/10.1016/S0304-3959(03)00301-4

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain*, *111*(1–2), 77–83. https://doi.org/10.1016/j.pain.2004.06.002

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Moscou-Jackson, G., Finan, P. H., Campbell, C. M., Smyth, J. M., & Haythornthwaite, J. A. (2015). The effect of sleep continuity on pain in adults with sickle cell disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010

Norman, B. J., & Miller, S. D. (2011). Human genome project and sickle cell disease. *Social*

Work in Public Health, *26*(4), 405–416. https://doi.org/10.1080/19371918.2011.579488 [doi]

Oliveira, V. C., Ferreira, P. H., Ferreira, M. L., Tiburcio, L., Pinto, R. Z., Oliveira, W., & Dias, R. (2009). People with low back pain who have externalised beliefs need to see greater improvements in symptoms to consider exercises worthwhile: an observational study. *The Australian Journal of Physiotherapy*, *55*(4), 271–275.

Oram, S., Ostrovschi, N. V, Gorceag, V. I., Hotineanu, M. A., Gorceag, L., Trigub, C., & Abas, M. (2012). Physical health symptoms reported by trafficked women receiving post-trafficking support in Moldova: prevalence, severity and associated factors. *BMC Women's Health*, *12*, 20. https://doi.org/10.1186/1472-6874-12-20

Park, J., & Chung, J. (2016). Inflammatory Cytokines and Sleep Disturbance in Patients with Temporomandibular Disorders. *Journal of Oral & Facial Pain and Headache*, *30*(1), 27–33. https://doi.org/10.11607/ofph.1367

Pavlin, D. J., Sullivan, M. J. L., Freund, P. R., & Roesen, K. (2005). Catastrophizing: a risk factor for postsurgical pain. *The Clinical Journal of Pain*, *21*(1), 83–90.

Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states--maybe it is all in their head. *Best Practice & Research.Clinical Rheumatology*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005 [doi]

Platt, O. S., Thorington, B. D., Brambilla, D. J., Milner, P. F., Rosse, W. F., Vichinsky, E., & Kinney, T. R. (1991). Pain in sickle cell disease. Rates and risk factors. *The New England Journal of Medicine*, *325*(1), 11–16. https://doi.org/10.1056/NEJM199107043250103 [doi]

Quartana, P. J., & Edwards, R. R. (2009). Pain catastrophizing : a critical review, *9*(5), 745–758.

Robinson, L. J., Durham, J., & Newton, J. L. (2016). A systematic review of the comorbidity between Temporomandibular Disorders and Chronic Fatigue Syndrome. *Journal of Oral Rehabilitation*, *43*(4), 306–316. https://doi.org/10.1111/joor.12367

Schaible, H.-G. (2014). Nociceptive neurons detect cytokines in arthritis. *Arthritis Research & Therapy*, *16*(5), 470.

Schlenz, A. M., Schatz, J., & Roberts, C. W. (2016). Examining Biopsychosocial Factors in Relation to Multiple Pain Features in Pediatric Sickle Cell Disease. *Journal of Pediatric Psychology*, *41*(8), 930–940. https://doi.org/10.1093/jpepsy/jsw003 [doi]

Schofferman, J., Anderson, D., Hines, R., Smith, G., & Keane, G. (1993). Childhood psychological trauma and chronic refractory low-back pain. *The Clinical Journal of Pain*, *9*(4), 260–265.

Severeijns, R., Vlaeyen, J. W., van den Hout, M. A., & Weber, W. E. (2001). Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *The Clinical Journal of Pain*, *17*(2), 165–172.

Shattuck, E. C., & Muehlenbein, M. P. (2016). Towards an integrative picture of human sickness behavior. *Brain, Behavior, and Immunity*, *57*, 255–262. https://doi.org/10.1016/j.bbi.2016.05.002

Sil, S, Cohen, L. L., & Dampier, C. (2016). Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *The Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289 [doi]

Sil, S, Dampier, C., & Cohen, L. L. (2016). Pediatric Sickle Cell Disease and Parent and Child Catastrophizing. *Journal of Pain*, *17*(9), 963–971. https://doi.org/10.1016/j.jpain.2016.05.008

Sil, Soumitri, Cohen, L. L., & Dampier, C. (2016). Psychosocial and functional outcomes in youth with chronic sickle cell pain. *Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289

Slade, G. D., Smith, S. B., Zaykin, D. V, Tchivileva, I. E., Gibson, D. G., Yuryev, A., … Diatchenko, L. (2013). Facial pain with localized and widespread manifestations: separate pathways of vulnerability. *Pain*, *154*(11), 2335–2343. https://doi.org/10.1016/j.pain.2013.07.009

Smith, S. B., Maixner, D. W., Fillingim, R. B., Slade, G., Gracely, R. H., Ambrose, K., … Diatchenko, L. (2012). Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. *Arthritis and Rheumatism*, *64*(2), 584–593. https://doi.org/10.1002/art.33338

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., Mcclish, D. K., & Roberts, J. D. (2008). Daily Assessment of Pain in Adults with Sickle Cell Disease. *Annals of Internal Medicine*, *148*, 94–101. https://doi.org/10.7326/0003-4819-148-2-200801150-00004

Smith, W. R., & Scherer, M. (2010). Sickle-cell pain: advances in epidemiology and etiology. *Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program*. https://doi.org/10.1182/asheducation-2010.1.409

Smith, Y. R., Stohler, C. S., Nichols, T. E., Bueller, J. A., Koeppe, R. A., & Zubieta, J.-K. (2006). Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(21), 5777–5785. https://doi.org/10.1523/JNEUROSCI.5223-05.2006

Snelling, J. (1994). The effect of chronic pain on the family unit. *Journal of Advanced Nursing*, *19*(3), 543–551.

Spiegel, D. R., Chatterjee, A., McCroskey, A. L., Ahmadi, T., Simmelink, D., Oldfield 4th, E. C., … Raulli, O. (2015). A Review of Select Centralized Pain Syndromes: Relationship With Childhood Sexual Abuse, Opiate Prescribing, and Treatment Implications for the Primary Care Physician. *Health Services Research and Managerial Epidemiology*, *2*, 2333392814567920-Dec. https://doi.org/10.1177/2333392814567920 [doi]

Spinhoven, P., Ter Kuile, M., Kole-Snijders, A. M. J., Hutten Mansfeld, M., Den Ouden, D.-J., & Vlaeyen, J. W. S. (2004). Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *European Journal of Pain*, *8*(3), 211–219. https://doi.org/10.1016/j.ejpain.2003.08.003

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D. B., & Paulus, M. P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry*, *65*(11), 1275–1284. https://doi.org/10.1001/archpsyc.65.11.1275

Thomas, L. S., Stephenson, N., Swanson, M., Jesse, D. E., & Brown, S. (2013). A pilot study: the effect of healing touch on anxiety, stress, pain, pain medication usage, and physiological measures in hospitalized sickle cell disease adults experiencing a vaso-occlusive pain episode. *Journal of Holistic Nursing*, *31*(4), 234–247. https://doi.org/10.1177/0898010113491631

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., … Watanabe, M. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The Journal of Pain : Official Journal of the American Pain Society*, *9*(10), 883–891. https://doi.org/10.1016/j.jpain.2008.05.005

Vacca Jr, V. M., & Blank, L. (2017). Sickle cell disease: Where are we now? *Nursing*, *47*(4), 26–34. https://doi.org/10.1097/01.NURSE.0000513609.79270.74 [doi]

Wakefield, E. O., Popp, J. M., Dale, L. P., Santanelli, J. P., Pantaleao, A., & Zempsky, W. T. (2017). Perceived Racial Bias and Health-Related Stigma Among Youth with Sickle Cell Disease. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *38*(2), 129–134. https://doi.org/10.1097/DBP.0000000000000381 [doi]

Wallen, G. R., Minniti, C. P., Krumlauf, M., Eckes, E., Allen, D., Oguhebe, A., … Taylor, J. G. (2014). Sleep disturbance, depression and pain in adults with sickle cell disease. *BMC Psychiatry*, *14*, 207. https://doi.org/10.1186/1471-244X-14-207

Wasserman, R. A., Brummett, C. M., Goesling, J., Tsodikov, A., & Hassett, A. L. (2014). Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Regional Anesthesia and Pain Medicine*, *39*(1), 13–17. https://doi.org/10.1097/AAP.0000000000000024 [doi]

Williams, D. A. (2018). Phenotypic features of central sensitization. *Journal of Applied Biobehavioral Research*, *23*(2), 1–15. https://doi.org/10.1111/jabr.12135

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(SUPPL.3). https://doi.org/10.1016/j.pain.2010.09.030

Zaza, C., & Baine, N. (2002). Cancer pain and psychosocial factors: a critical review of the literature. *Journal of Pain and Symptom Management*, *24*(5), 526–542.

Zempsky, W T, Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread Pain Among Youth With Sickle Cell Disease Hospitalized With Vasoocclusive Pain: A Different Clinical Phenotype? *The Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403 [doi]

Zempsky, William T., Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread pain among youth with sickle cell disease hospitalized with vasoocclusive pain. *Clinical Journal of Pain*, *33*(4), 335–339.

https://doi.org/10.1097/AJP.0000000000000403

Zempsky, William T. (2009). Treatment of sickle cell pain: fostering trust and justice. *JAMA*, *302*(22), 2479–2480. https://doi.org/10.1001/jama.2009.1811

CHAPTER II

Review of the Literature

This chapter begins with an overview of pain definitions, incidence, characteristics, pathophysiology, and influencers (physiological, psychological, and situational). This is followed by a literature synthesis of research studies involving patients with sickle cell disease (SCD), an evaluation of the level of evidence, and an explanation of the gaps in the current science. The chapter will conclude with a summary of the gaps that will be addressed by this dissertation study.

Introduction

Pain is a significant problem within the United States. In 2012, the National Center for Health Statistics, Center for Disease Control and Prevention reported that 86.6 million adults had pain on some days and 25.5 million had pain every day (Adams, Kirzinger, & Martinez, 2013; Medicine, 2011; Nahin, 2015). Additionally, pain costs the nation up to $635 billion each year (Medicine, 2011). Despite its profound impact, there are limited effective treatments for chronic pain. Further, pharmacologic interventions do not address the complex, inter-related multidimensional physiological, psychological, and situational mechanisms of pain (Lenz et al., 1997). With better knowledge of pain mechanisms, targeted interventions can be developed and tested to reduce the myriad of negative sequelae caused by uncontrolled pain (e.g., anxiety, depression, increased healthcare costs) (Robinson, Katon, Kroenke, 2003; Medicine, 2011; Wade, Price, Hamer, Schwartz, & Hart, 1990). Thus, theory-driven research that explores the

multidimensional mechanisms of pain perception is needed to improve the lives of patients with daily pain.

Types of Pain

Pain is defined as "the unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of damage" (Merskey & Bogduk, 1994). There are three pain types that will be discussed within this section: nociceptive pain, neuropathic pain, and nociplastic pain. The following paragraphs outline specific mechanism definitions and characteristics.

Nociceptive pain is a painful experience that is short lived with varying intensity and can be caused by tissue or bone injury resulting from trauma, surgery, and acute medical conditions for example, bone fractures, appendicitis, and nephrolithiasis (Carr & Goudas, 2013; Nicholson, 2006). Nociceptive pain is characterized by sharp, aching, and pressure sensations.

Unlike nociceptive pain, neuropathic pain (NP) occurs as a result of nerve injury in the periphery or the central nervous system (CNS), and can be acute or chronic (Woolf, 2010). One cause of acute NP is surgery-associated axillary or intercostobrachial nerve damage that occurs following procedures to manage breast cancer: mastectomy, lumpectomy, axillary node dissection, and breast reconstruction. This acute nerve damage results in pain in the axilla, inner side of the upper arm, and shoulder (Andersen, Aasvang, Kroman, & Kehlet, 2014; Smith et al., 2014). Chronic pain is defined as pain that continues past the normal time of healing (Merskey & Bogduk, 1994). The normal time of healing may vary based on the origin of injury; however, many categorize chronic pain as pain that has lasted longer than three to six months. Causes of chronic NP include acute intervertebral disc herniation, cerebrovascular accident, acute herpes,

among others (Dubin & Patapoutian, 2010; Woolf, 2010). Common clinical manifestations of NP include shooting, burning, numbness, and tingling.

A third type of pain, nociplastic pain (also termed centralized pain), has been described by the International Association for the Study of Pain (IASP) as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (2017). Thus, unlike nociceptive and neuropathic pain, centralized pain can occur without any damage to the peripheral or central nervous systems. Despite minimal or no damage, patients with centralized pain may experience with hyperalgesia (increased pain sensitivity), allodynia (pain perception due to a normally non-painful stimulus), widespread pain, numbness, burning, and tingling (Bridges, Thompson, & Rice, 2001; Latremoliere & Woolf, 2009). The following section will include detailed information regarding nociceptive pathways and pain perception.

Nociceptive Pathways

Nociception is defined as the "neural process of encoding noxious stimuli" (IASP, 2017). Several different neural processes make up the nociceptive system to warn the body of actual or imminent damage. The nociceptive system provides neural signals to the central nervous system that may be interpreted as pain. The following section describes nociceptive processing within an individual who has a normally functioning and activated nociceptive system.

Transduction and Transmission.

First, sensory fibers located throughout the body alert the nociceptive system of potentially dangerous stimuli via electrical signals (McEntire et al., 2016). This process is often referred to as transduction and transmission. Transduction refers to the conversion of noxious

stimuli into electrical signals via sensory nerve fibers (McEntire et al., 2016). There are two types of sensory, or afferent, nerve fibers: thinly myelinated Aδ and unmyelinated C fibers. Peripheral tissue damage, resulting from noxious stimuli (e.g., thermal, mechanical, or chemical stimuli), causes the release of several chemical substances including serotonin, bradykinin, histamine, histamine, prostaglandins, and substance P (McEntire et al., 2016). These substances activate the afferent nerve fibers via serotonin (5-HT) receptors and relevant acid-sensing (ASIC), transient receptor potential (TRP), and voltage-gated sodium (Nav) ion channels, among others (McEntire et al., 2016). The opening and activation of sodium ion channels eventually leads to depolarization of an action potential. Transmission refers to the nociceptive process in which the action potential travels along the afferent nerve fiber axon to the dorsal horn within the spinal cord (Dubin & Patapoutian, 2010; Marchand, 2008). These afferent nerve fibers ultimately terminate in the dorsal horn within the spinal cord (Dubin & Patapoutian, 2010; Marchand, 2008).

Modulation.

The third step in the nociceptive pathway is modulation. Modulation refers to activity within the CNS that either inhibits or enhances the transmitted input from the periphery (Marchand, 2008). Excitatory neurons, inhibitory neurons, and projection cells within the dorsal horn influence whether the action potential is transmitted from the periphery to the brain (Alves & Lin, 2018). These neurons have both excitatory and inhibitory receptors that are activated by neurotransmitters, leading to the overall inhibition or excitation within the dorsal horn (Alves & Lin, 2018).

Inhibition is enhanced via the descending pathway, which involves multiple neuron synapses within the brain, rostral ventromedial medulla (RVM), and spinal cord (Dubin &

Patapoutian, 2010; Holden, Jeong, & Forrest, 2005). Bidirectional modulation occurs in the RVM. Specifically, within the RVM, neurons are frequently referred to as "on" (pronociceptive) and "off" (antinociceptive) cells. These cells can increase or decrease their projections to the spinal cord, thus impacting overall excitation or inhibition (Aicher, Hermes, Whittier, & Hegarty, 2012; Burgess et al., 2002; Ossipov, Dussor, & Porreca, 2010). Further, evidence suggests that stimulation of the periaqueductal gray region (PAG) or RVM causes the release of the following endogenous opioid peptides: enkephalins, dynorphins, endorphin, serotonin, and norepinephrine (Holden et al., 2005; Ossipov et al., 2010). These peptides act as neurotransmitters and bind to inhibitory pain receptors within the dorsal horn, producing analgesia (Holden et al., 2005; Ossipov et al., 2010).

If excitation within the dorsal horn is greater than inhibition, the nerve impulse will be transmitted to the brain via ascending tracts (Albe-Fessard, Berkley, Kruger, Ralston, & Willis, 1985; Alves & Lin, 2018; Flor & Turk, 2011; Schaibl & Richter, 2004). The spinothalamic tract is the major pathway for transmission of nociceptive input from the spinal cord to several supraspinal areas including: the RVM, PAG, thalamus, amygdala, insular cortex, somatosensory cortex, prefrontal cortex, and anterior cingulate cortices (Albe-Fessard et al., 1985; Dubin & Patapoutian, 2010; Jones, 1999; Marchand, 2008).

Pain Perception.

The fourth and final step in the nociceptive processing pathway occurs when the patient perceives the nociceptive input as pain (Dubin & Patapoutian, 2010; Marchand, 2008). As previously discussed, once a nerve impulse is transmitted from the dorsal horn, it travels to several areas in the brain. Within these supraspinal areas (e.g., the amygdala, hypothalamus, periaqueductal grey, and basal ganglia), cognitive processes lend meaning to nociceptive stimuli

(Garland, 2012). Specifically, pain perception involves a conscious evaluation of the sensory signals (cognitive appraisal), attention to pain, and emotional and behavioral reactions to pain (Garland, 2012). A child with SCD, who is distracted by coloring, may perceive their pain as less intense compared to a child who is alone in their room and focusing on their pain. This example highlights the subjectivity of pain and its dependence on a variety of influencing factors. A thorough description of various factors that influence pain perception is provided later in this chapter.

Neuropathic and Centralized Pain Pathophysiology

In the previous section, four general physiologic processes were described: transduction, transmission, modulation, and perception. In this next section, the focus will be on the unique pathophysiologic mechanisms involved in the development of pain in neuropathic and centralized pain states.

Neuropathic Pain.

Multiple pathophysiologic mechanisms can lead to the development of neuropathic pain. First, neuropathic pain occurs following peripheral or central nervous system tissue damage in the following areas: peripheral nerve, nerve root, and spinal cord (Baron, Binder, & Wasner, 2010). Following nerve tissue injury, nerve growth factors are released from injured neurons facilitating the growth of new dendrites on the nerve (Cohen & Mao, 2014). An increase in dendrites causes an expansion in the receptive field of the nerve, increasing its susceptibility to stimulation, or hyperalgesia (Baron et al., 2010; Cohen & Mao, 2014). Further, lesions on the injured nerve can generate spontaneous, or ectopic, nerve activity (Baron et al., 2010; Latremoliere & Woolf, 2009; Woolf, 2011). Crosstalk between different types of nerve fibers, nociceptive, C and Aδ, and non-nociceptive, Aβ, also leads to the clinical characteristics of

allodynia and secondary hyperalgesia (Baron et al., 2010; Cohen & Mao, 2014; Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Ueda, 2008).

As previously described, ectopic activity of afferent nerve fibers occurs following nerve injury. After injury, localized edema occurs after the release of several inflammatory mediators including substance P and calcitonin gene related peptide. Several other byproducts, for example bradykinin, prostaglandins, and cytokines, are also released following the inflammatory mediators (Cohen & Mao, 2014; Thacker, Clark, Marchand, & McMahon, 2007). Together, these substances sensitize and excite afferent nerve fibers, resulting in decreased pain thresholds and ectopic discharges (Cohen & Mao, 2014). Additionally, after nerve injury, there is an increased expression of calcium channels within sensory and dorsal horn neurons. Increased expression of calcium channels results in increased membrane depolarization and hyperpolarization among afferent nerve fibers (Cohen & Mao, 2014; Perret & Luo, 2009; Thacker et al., 2007; West, Bannister, Dickenson, & Bennett, 2015). Lastly, evidence suggests that spontaneous pain arises from both ectopic activity in primary afferent nerve fibers and central sensitization (Costigan, Scholz, & Woolf, 2009). A description of central sensitization is provided in the following section.

Centralized Pain.

As previously described, centralized pain arises from altered nociception with minimal or no tissue damage or evidence for disease or lesion of the somatosensory system (Latremoliere & Woolf, 2009; Marchand, 2008; Woolf, 2011). Some examples of centralized pain conditions are fibromyalgia, irritable bowel syndrome, temporomandibular disorder, and urinary chronic pain pelvic syndromes. Central sensitization is a term used to describe the mechanisms that can contribute to centralized pain states. Central sensitization is defined as “increased responsiveness

of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (IASP, 2017). Manifestations of central sensitization include hyperalgesia, secondary hyperalgesia, and allodynia (Harte, Harris, & Clauw, 2018; Latremoliere & Woolf, 2009; Woolf, 2011). Central sensitization can occur with or without ongoing nociceptive input (Harte et al., 2018). When ongoing nociceptive input is absent, the process is hypothesized to originate in supraspinal structures (Harte et al., 2018).

Several supraspinal mechanisms that maintain centralized pain states have been studied (Harris et al., 2007; Napadow et al., 2010; Sarchielli et al., 2007). One study in patients with fibromyalgia identified a decreased availability of central μ-opioid receptors within several areas of the brain that are known to play a role in pain modulation (Harris et al., 2007). Decreased availability of these inhibitory receptors further increases the likelihood of pain transmission (Harris et al., 2007). Therefore, patients with centralized pain may have several chemical alterations that augment pain facilitation and attenuate pain modulation without the presence of actual or threatened tissue damage.

Neuroplasticity within supraspinal regions is another mechanism that can maintain centralized pain. In patients with centralized pain, pro-nociceptive neuroplastic changes have been identified within the medial prefrontal cortex, RVM, thalamus, and default mode network (Darbari et al., 2015; Kucyi et al., 2014; Mansour, Farmer, Baliki, & Apkarian, 2014). Increased connectivity, cortical reorganization, and decreased gray matter have been demonstrated via structural brain imaging in several centralized pain populations including irritable bowel syndrome, fibromyalgia, chronic low back pain, and SCD (Darbari et al., 2015; Mansour et al., 2016; May, 2008; Napadow et al., 2010). One study in patients with SCD identified that patients with increased pain frequency had increased pro-nociceptive brain connectivity, while patients

with decreased pain frequency had increased anti-nociceptive brain connectivity (Darbari et al., 2015).

Pain Influencing Factors

Several physiological, psychological, and situational factors contribute to the perception of pain. Within this section, I will describe the impact these factors have on pain processing mechanisms and pain-related outcomes among patients with centralized pain.

Physiological.

Genetics.

Empirical evidence suggests that individuals may have a genetic predisposition to developing centralized pain (Diatchenko et al., 2005; Emin Erdal et al., 2001; Gursoy et al., 2003; S. B. Smith et al., 2012). Recent research has sought to evaluate differences in gene frequencies among patients with and without centralized pain. Several studies have identified gene frequency differences in patients with fibromyalgia, temporomandibular disorders, and migraine compared to healthy controls (Diatchenko et al., 2005; Emin Erdal et al., 2001; Gursoy et al., 2003; S. B. Smith et al., 2012). Further, the presence of genetic polymorphisms may also influence pain transmission, perception, and analgesic response. Specifically, catechol-*O*-methyltransferase (COMT) is an enzyme that inactivates modulatory neurotransmitters including dopamine, norepinephrine, and epinephrine. Empirical evidence suggests that COMT variations influence susceptibility to pain conditions, pain sensitivity, and opioid response (Andersen & Skorpen, 2009; Diatchenko et al., 2005).. Individuals with the 108/158Met allele of COMT have higher levels of dopamine within the prefrontal cortex resulting in increased pain sensitivity and decreased activation of the μ-opioid system after continuous painful stimuli (Andersen & Skorpen, 2009).

Sex.

Evidence supports differences in pain perception between males and females (Bartley & Fillingim, 2013; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009). Specifically, females have increased pain incidence, sensitivity, and duration compared to males (Fillingim et al., 2009). Pain sensitivity, pain modulation, and cortical activation are influenced by pro- or anti-nociceptive sex hormones including progesterone and oestradiol, among others (Bartley & Fillingim, 2013; Fillingim et al., 2009). Specifically, evidence suggests differences in pain sensitivity during different phases of the menstrual cycle (Bartley & Fillingim, 2013; Smith et al., 2006). One study highlighted that women in a low oestradiol, low progesterone state report increased pain sensitivity (Smith et al., 2006).

Age.

Age is another physiologic influencing factor that has been studied within several pain populations. Evidence suggests that middle and older age groups have the highest prevalence of centralized pain and increased multifocal pain, incidence, and intensity (Fayaz, Croft, Langford, Donaldson, & Jones, 2016; Helme & Gibson, 2001; Krueger & Stone, 2008; Rustoen et al., 2005). Several physiologic processes may influence age differences in pain including reduced peripheral nerve fibers, decreased sensory neurons within the dorsal root ganglion, and inflammation, among others (Gagliese, 2009; Yezierski, 2013). Much of this research, however, is limited to animal models (Gagliese, 2009). Although it is known that pain increases with age, future research is needed to determine the mechanisms that influence these differences.

Fatigue.

Evidence supports the co-occurrence of several centrally-mediated symptoms among patients with centralized pain syndromes (Clauw & Chrousos, 1997; Phillips & Clauw, 2011). First, several studies have highlighted an association between fatigue and pain (Garip, Eser, Aktekin, & Bodur, 2011; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Pollard, Choy, Gonzalez, Khoshaba, & Scott, 2006). Several body systems that influence pain including the endocrine, central nervous, peripheral nervous, and immune systems also exacerbate fatigue (Louati & Berenbaum, 2016). Specifically, fatigue and pain have both been associated with the following increased inflammatory cytokines: interleukin (IL)-1β, IL-6, IL-17 and tumor necrosis factor (TNF)-α (Bower, 2014; Schaible, 2014). One cohort study including 1,466 patients with advanced cancer showed a positive association between C-reactive protein (CRP) levels, pain, and fatigue (Laird et al., 2013). Further, increased IL-8 and IL-2r levels have also been identified in patients with fibromyalgia, suggesting a shared physiologic mechanism between fatigue and centralized pain (Gur et al., 2002).

Sleep.

Another centrally-mediated symptom that co-occurs with pain is sleep impairment. Although sleep quality and sleep disturbances have been shown to influence pain (Allen, Renner, Devellis, Helmick, & Jordan, 2008; Campbell et al., 2011; Edwards, Almeida, Klick, Haythornthwaite, & Smith, 2008; Palermo & Kiska, 2005; Wolfe, Michaud, & Li, 2006), sleep duration may not be impacted among individuals with centralized pain. Patients may, however, report sleep as nonrestorative, or the subjective feeling of being unrefreshed upon awakening despite the appearance of physiologically normal sleep (Stone, Taylor, McCrae, Kalsekar, & Lichstein, 2008).

Dopaminergic signaling and cytokine activity are two mechanisms in which pain and sleep impairment are hypothesized to relate to each other (Campbell et al., 2011; Finan, Goodin, & Smith, 2014; Taylor, Becker, Schweinhardt, & Cahill, 2016). Dopamine, an inhibitory pain neurotransmitter, also plays a role in sleep regulation via the promotion and maintenance of arousal states. Although it is known that patients with centralized pain have lowered dopamine (D2) receptor binding and presynaptic dopamine activity (Finan et al., 2014; Taylor et al., 2016), future research is needed to determine the specific underlying dopaminergic mechanisms that influence sleep impairments (Finan et al., 2014).

The immune system is also hypothesized to influence the relationship between sleep and pain. Like fatigue, increasing evidence suggests that cytokine activity and pain are interrelated (Heffner et al., 2011; Park & Chung, 2016). Studies conducted among patients with centralized pain have highlighted the bidirectional associations among sleep, pain, and the following proinflammatory cytokines: IL-1β, IL-6, IL-10, and TNF-α (Heffner et al., 2011; Park & Chung, 2016). Sleep quality has been shown to mediate the relationship between pain intensity and IL-6 levels in patients with chronic low back pain (Heffner et al., 2011). Further, research suggests positive relationships among daytime sleepiness, poor sleep quality, cytokine levels, pain intensity, and pain duration in patients with TMD (Park & Chung, 2016).

Psychological.

Depression.

As discussed within the centralized pain pathophysiology section, centralized pain can be maintained via changes within supraspinal regions that are responsible for pain processing. As in centralized pain, structural and functional changes have been identified in patients with depression within the following brain areas: the dorsolateral prefrontal cortex, lateral-orbital

prefrontal cortex, medial prefrontal cortex, insula, anterior cingulate cortex, amygdala, hippocampus, and thalamus (Maletic & Raison, 2009). Given that depression and pain perception emerge due to activity in similar cortical regions, these two symptoms may have shared physiologic mechanisms, such that depression and pain may give rise to and exacerbate the other. (Maletic & Raison, 2009; Strigo et al., 2008). Evidence suggests that patients with depression have increased activation of the dorsolateral and ventrolateral prefrontal cortices, amygdala, insula, and dorsolateral anterior cingulate cortex when responding to or anticipating pain (Bar et al., 2005; Strigo et al., 2008). Further, patients with depression have decreased activation of areas within the descending pain modulatory pathway, for example the rostral anterior cingulate cortex and PAG (Strigo et al., 2008). Decreased activation of these supraspinal areas leads to a decreased ability to inhibit pain (Maletic & Raison, 2009; Strigo et al., 2008).

Anxiety.

Another psychological factor that has been shown to influence pain is anxiety. Evidence suggests that anxiety is strongly associated with several centralized pain conditions (e.g., chronic back pain and migraine) (Davis et al., 2017; Hanks & LLOYD, 1986; McWilliams et al., 2003, 2004; Tsang et al., 2008). Anxiety responses also occur within brain areas that perceive pain including the amygdala and several cortices: anterior cingulate, posterior cingulate, and orbitofrontal (Etkin, Egner, & Kalisch, 2011; Gross & Hen, 2004). Evidence suggests a positive relationship between anxiety and increased activation of several pain processing mechanisms within the brain including the anterior cingulate, posterior cingulate, and orbitofrontal cortices (Kalisch et al., 2005; Ochsner et al., 2006).

Catastrophizing.

Catastrophizing occurs when a patient has irrational thoughts about their pain including rumination, magnification and helplessness (Citero et al., 2007; Quartana & Edwards, 2009). Pain catastrophizing is often described as an exaggerated, negative cognitive-affective response to current or anticipated pain (Quartana & Edwards, 2009). Multiple studies support that catastrophizing is associated with pain-related outcomes (Ciechanowski et al., 2003; Geisser et al., 1994; Keefe et al., 2000; Pavlin et al., 2005; Quartana & Edwards, 2009; Severeijns et al., 2001). Additionally, research has identified an association between pain catastrophizing and increased activation of the following pain processing areas: dorsolateral prefrontal cortex, anterior cingulate cortex, and medial prefrontal cortex (Quartana & Edwards, 2009). Pain catastrophizing may also have an impact on pain inhibition. In summation, these findings suggest that pain catastrophizing is associated with development and maintenance of pain.

Pain control beliefs.

The last psychological variable included in this review is pain control beliefs. These include beliefs about internal or external locus of pain control. Patients with internal locus of control beliefs think that they have the ability to control their pain (Skevington, 1990). On the other hand, a patient with external locus of control beliefs thinks that their pain is controlled by others or by chance (Skevington, 1990). Beliefs about pain control can influence how a patient processes, treats, and copes with pain (Higgins et al., 2015; Oliveira et al., 2009; Spinhoven et al., 2004).

Situational.

Stigma.

Lack of objective evidence of pain (e.g., bandages, fractures, facial grimaces) can lead to stigmatization among patients with centralized pain. Empirical evidence suggests that patients with centralized pain may experience stigmatization from multiple sources including health care providers, family members, teachers, and peers, among others (Kool, van Middendorp, Boeije, & Geenen, 2009; Logan, Catanese, Coakley, & Scharff, 2007; Monsivais, 2013; Wakefield, Zempsky, Puhl, & Litt, 2018). Further, stigmatization has been associated with delayed diagnosis or misdiagnosis, bias in treatment, social isolation, increased pain burden, and lower quality of life (NINDS, 2015; Wakefield et al., 2018).

Trauma exposure.

Pain research suggests significant relationships among trauma exposure, the development of centralized pain, and increased pain severity and interference (Hauser, Kosseva, Uceyler, Klose, & Sommer, 2011; Kanzawa-Lee et al., 2018; Oram et al., 2012; Phillips & Clauw, 2011; Schofferman, Anderson, Hines, Smith, & Keane, 1993; Spiegel et al., 2015). Evidence supports significant associations between the incidence of fibromyalgia and self-reported physical and sexual abuse in childhood and adulthood (W Hauser et al., 2011). Further, sex-variations in pain perception may be present following trauma exposure (Bartley & Fillingim, 2013; Fillingim et al., 2009). Specifically, females are more likely to have decreased pain sensitivity following trauma exposure compared to men (Bartley & Fillingim, 2013; Fillingim et al., 2009).

Social support.

The last situational variable included in this review is social support. Those with centralized pain often elicit passive coping strategies that negatively influence social support

systems, for example self-imposed isolation and victimization (Forgeron et al., 2010; Smith & Osborn, 2007; Snelling, 1994; Zaza & Baine, 2002). Additionally, patients with centralized pain may have difficulty maintaining friendships (Carter et al., 2002). Researchers agree that the presence of centralized pain negatively influences the availability of social support systems; however, there is conflicting evidence regarding the relationship of social support and pain-related outcomes (e.g., pain intensity, frequency, and sensitivity) (Lopez-Martinez, Esteve-Zarazaga, & Ramirez-Maestre, 2008; Montoya, Larbig, Braun, Preissl, & Birbaumer, 2004; Smite, Rudzite, & Ancane, 2012). Two research studies demonstrated a significant association between increased perceived social support and decreased pain intensity and interference (Lopez-Martinez et al., 2008; Smite et al., 2012). Additionally, patients with fibromyalgia had significantly decreased pain sensitivity in the presence of significant others (Montoya et al., 2004).

Active coping strategies can also mediate the relationship between social support and pain (Holtzman et al., 2004). Specifically, evidence suggests that patients with centralized pain that have increased social support receive more encouragement to use active coping strategies that decrease their pain (Holtzman et al., 2004).

Cognitive.

Cognitive function.

The relationship between centralized pain and cognitive function is beginning to gain recognition within the literature (Williams, 2018). Evidence suggests that cognition can be grouped in a symptom cluster along with sleep, pain, affect (e.g., depression and anxiety), and energy deficit (fatigue), or S.P.A.C.E (Schrepf et al., 2018; D. A. Williams, 2018). These symptoms are hypothesized to interact with each other via a shared physiologic mechanism—the

immune system (Heffner et al., 2011; Park & Chung, 2016; Schaible, 2014). As discussed previously, increased levels of cytokines including IL-1β, IL-6, IL-8, and TNF-α, among others, are associated with increased levels of pain, fatigue, and sleep disturbance (Heffner et al., 2011; Park & Chung, 2016; Schaible, 2014). One meta-analysis supports that IL-1β and IL-6 have significant relationships with the S.P.A.C.E. symptom cluster (Shattuck & Muehlenbein, 2016). However, cognitive function is an understudied symptom within this cluster. Although associations have been found between different cytokine levels and cognitive impairment, further research is needed to clarify this relationship (Shattuck & Muehlenbein, 2016).

Pain in Sickle Cell Disease

Thus far, this chapter has provided an overview of pain definitions, incidence, characteristics, pathophysiology, and influencing factors. What follows is an expanded discussion of the unique pain manifestations that are commonly observed in patients with SCD. A synthesis of empirical evidence from randomized controlled trials (RCTs) of pharmacologic and non-pharmacologic treatments is also presented. The chapter will conclude with a summary of the gaps identified within the literature that are addressed by this dissertation study.

While acute pain/VOC has been recognized as a common complication of SCD, recent evidence suggests that a subset of patients with SCD have centralized pain (Brandow, Farley, & Panepinto, 2015; Brandow, Farley, & Panepinto, 2014; Brandow & Panepinto, 2016; Brandow, Stucky, Hillery, Hoffmann, & Panepinto, 2013; Campbell et al., 2016; Carroll et al., 2016; Jacob et al., 2015; O'Leary, Crawford, Odame, Shorten, & McGrath, 2013; Smith & Scherer, 2010; Wilkie et al., 2010). One study identified that centralized pain occurs in 37% of patients with SCD (Brandow et al., 2015). Additionally, 21.8% of youth with SCD have multifocal pain (Zempsky et al., 2017), a common manifestation of centralized pain. Quantitative Sensory

Testing (QST) methods have identified that patients with SCD have impaired pain processing manifested as decreased thermal and mechanical pain thresholds (Brandow & Panepinto, 2016; Campbell et al., 2016; Jacob et al., 2015). Further, patients with centralized pain have increased VOCs, pain intensity, and pain severity compared to patients without centralized pain (Campbell et al., 2016; Zempsky et al., 2017).

Based upon the deep discussion of pain influencing factors described earlier within this chapter, it is clear that several physiological, psychological, situational, and cognitive factors co-occur to influence pain among those with centralized pain. However, there is a lack of understanding about how these factors influence pain among those with SCD. The following section will synthesize the literature regarding several influencing factors that influence pain among those with SCD.

Pain-Influencing Factors in Patients with SCD

Articles published within the past 10 years were reviewed and synthesized. Joanna Briggs Institute (JBI) critical appraisal tools were used to evaluate each studies' methodological design and potential risks of bias (Joanna Briggs Institute Critical Appraisal Tools, 2017). Detailed information regarding the methodological design, findings, and critical appraisal of each study is provided within Appendices 1-5.

Physiological.

Genetics.

Pain in patients with SCD co-occurs with several physiological factors. First, genetic factors may contribute to pain-related outcomes in patients with SCD. Seven studies have evaluated the relationships among SCD genotype, multifocal pain, sensitivity, opioid use, health service utilization, pain intensity, and pain frequency (Carroll et al., 2016; Carroll, Haywood,

Hoot, & Lanzkron, 2013; Jacob et al., 2015; McClish et al., 2009; Schlenz, Schatz, & Roberts, 2016; Sil, Cohen, & Dampier, 2016; Zempsky et al., 2017). Out of the seven studies that have evaluated the relationship between SCD genotype and pain, six utilized cross-sectional study designs (Carroll et al., 2016; Carroll, Haywood, Hoot, & Lanzkron, 2013; Jacob et al., 2015; Schlenz, Schatz, & Roberts, 2016; Sil, Cohen, & Dampier, 2016; Zempsky et al., 2017). Only one of the cross-sectional studies reported significant differences in pain intensity based on SCD genotype (Schlenz et al., 2016) Patients with HbSS and HbSβ^0 had higher pain intensity ratings than those with HbSC and HbSβ^+ (Schlenz et al., 2016). This article, however, has limitations (Schlenz et al., 2016). First, its cross-sectional study design limits the ability to support a causal relationship between SCD genotype and pain intensity. Further, the pain history interview used within this study included retrospective reports of pain intensity, duration, and frequency which could be subject to recall bias. The remaining six articles highlighted no significant differences in multifocal pain, opioid use, health service utilization, pain intensity, pain sensitivity, and pain frequency based on SCD genotype (Carroll et al., 2016; Carroll et al., 2013; Jacob et al., 2015; McClish et al., 2009; Sil, Cohen, & Dampier, 2016; Zempsky et al., 2017). This suggests that the majority of evidence supports no differences in pain based upon SCD genotype.

Sex.

Although evidence suggests significant differences in pain perception between males and females (Bartley & Fillingim, 2013; Fillingim et al., 2009; Smith et al., 2006), there is conflicting evidence of sex differences among patient with SCD. Overall, ten studies evaluated the relationship between sex and pain (Antunes, Propheta, Vasconcelos, & Cipolotti, 2017; Bakshi, Lukombo, Belfer, & Krishnamurti, 2018; Bakshi, Lukombo, Shnol, Belfer, & Krishnamurti, 2017; Brandow et al., 2013; Carroll et al., 2016; Graves & Jacob, 2014; Jacob et

al., 2015; McClish et al., 2009; Sil et al., 2016; Zempsky et al., 2017). Three out of the ten studies found significant sex differences in pain sensitivity and severity among patients with SCD (N Bakshi et al., 2017; A M Brandow, Farley, & Panepinto, 2014; Graves & Jacob, 2014). Two studies identified that males have increased heat detection threshold and lower neuropathic pain scores compared to females (Bakshi et al., 2017; Brandow, Farley, & Panepinto, 2014). The third study evaluated the relationships among pain, coping, and sex, and found significant negative correlations between worst pain severity, positive behavioral distraction, and negative internalizing/catastrophizing among males (Graves & Jacob, 2014). These negative correlations were not evident in females (Graves & Jacob, 2014).

The three studies described above found significant sex differences in pain sensitivity and severity among patients with SCD (N Bakshi et al., 2017; A M Brandow et al., 2014; Graves & Jacob, 2014). These studies, however, had limitations which could have influenced their results. Graves & Jacob (2014) included a measure for pain frequency that asked parents of children with SCD to report the number of pain episodes that their child had within the past 12 months. An objective measure for pain frequency would have increased the reliability and validity of this outcome measure and reduced measurement error. Further, all of these studies evaluated multiple influencing factors along with sex including age, depression, anxiety, and catastrophization (Bakshi et al., 2017; Brandow et al., 2014; Graves & Jacob, 2014). Two of these studies, however, did not statistically correct for multiple comparisons (Bakshi et al., 2017; Graves & Jacob, 2014). This increases the likelihood that the significant differences found between males and females were due to chance.

Eight studies found no sex differences among a variety of pain manifestations—pain intensity, pain frequency, health care utilization, multifocal pain, neuropathic pain, and pain

thresholds assessed via QST (Antunes et al., 2017; Bakshi et al., 2018; Brandow et al., 2013; Carroll et al., 2016; Graves & Jacob, 2014; Jacob et al., 2015; McClish et al., 2009; Sil et al., 2016; Zempsky et al., 2017). Although these studies also had many limitations, this highlights that the majority of evidence supports no significant differences in pain between males and females with SCD.

Age.

It was previously discussed that widespread pain and pain intensity are associated with older age (Fayaz et al., 2016; Helme & Gibson, 2001; Krueger & Stone, 2008; Rustoen et al., 2005). Evidence also supports this association among patients with SCD. Twelve studies have evaluated the relationship between age and pain (Antunes et al., 2017; Bakshi et al., 2018, 2017; Brandow et al., 2014, 2013; Carroll et al., 2016; Carroll et al., 2013; Graves & Jacob, 2014; Jacob et al., 2015; McClish et al., 2009; Sil et al., 2016; Zempsky et al., 2017). Of those, seven studies have found significant associations between age and pain (Antunes et al., 2017; Bakshi et al., 2017; Brandow et al., 2014, 2013; Carroll et al., 2013; McClish et al., 2009; Sil et al., 2016). Five of these studies support significant associations between older age and increased widespread pain, pain frequency, neuropathic pain, and lower thermal and mechanical pain thresholds (Antunes et al., 2017; Bakshi et al., 2017; Brandow et al., 2013; McClish et al., 2009; Sil et al., 2016). One retrospective cohort study identified that patients of ages 18-30 had the highest emergency department visit, hospitalization, and re-hospitalization rates compared to all other age groups (Brousseau, Owens, Mosso, Panepinto, & Steiner, 2010). Further, one study conducted in adults found that age was significantly different between high and low health service utilization groups (Carroll et al., 2013). Those in the high utilization group had a mean age of 28.6, while those in the low group had a mean age of 38. It is hypothesized that those aged

18-30 are at an increased risk for health service utilization due to the transition from pediatric to adult care (Brousseau et al., 2010). The two longitudinal studies that evaluated the relationship between age and health service utilization rates included both pain and non-pain-related visits, which could have confounded the results and reduced the ability to detect a significant difference between age and pain-related visits (Brousseau et al., 2010; Carroll et al., 2013).

Although seven studies found a significant association among age, widespread pain, pain frequency, neuropathic pain, and lower pain thresholds, conflicting findings, descriptive study designs, and limitations reduce the strength of the evidence. Specifically, of the 12 studies, five studies highlighted no age differences based on opioid use, pain intensity, pain frequency, multifocal pain, and abnormal pain thresholds determined via QST (Bakshi et al., 2018; Carroll et al., 2016; Graves & Jacob, 2014; Jacob et al., 2015; Zempsky et al., 2017). Eight of the studies were cross-sectional (Antunes et al., 2017; N Bakshi et al., 2018; A M Brandow et al., 2014; P. C. Carroll et al., 2013; Graves & Jacob, 2014; Eufemia Jacob et al., 2015; S Sil, Cohen, et al., 2016; William T. Zempsky et al., 2017), two were longitudinal (C. P. Carroll et al., 2016a; McClish et al., 2009), and two was a case-control study (N Bakshi et al., 2017; Amanda M. Brandow et al., 2013). Two of the studies that reported significant results evaluated three or more influencing factors and did not statistically correct for multiple comparisons within their analyses (Bakshi et al., 2018; Carroll et al., 2013). This reduces the statistical conclusion validity of their results and increases the likelihood that the significant associations found between age and pain were due to chance. In summary, many of the studies reported above had limitations that influenced the internal and statistical conclusion validity of the studies. However, the majority of the evidence supports an association between older age and increased pain among patients with SCD.

Fatigue.

Another physiological factor that co-occurs with pain is fatigue (Garip et al., 2011; Nicassio et al., 2002; Pollard et al., 2006). Limited studies, however, have evaluated the association between fatigue and pain in patients with SCD. Only one study was found that identified a significant positive association between increased fatigue and increased pain intensity and interference measured via a reliable and valid pain measure, the Brief Pain Inventory (Ameringer et al., 2014). This study utilized a cross-sectional design limiting conclusions regarding the causal relationship between fatigue and pain. Further, the article did not include a detailed description of the study setting making it difficult to evaluate the internal validity of the study design. The lack of evidence regarding the relationship between fatigue and pain in patients with SCD highlights a gap within the literature regarding an important centrally-mediated symptom that is known to co-occur with pain.

Sleep.

The last physiological variable included in this review is sleep. Similar to other centralized pain populations including osteoarthritis, rheumatoid arthritis, and fibromyalgia (Allen, Renner, Devellis, Helmick, & Jordan, 2008; Campbell et al., 2011; Edwards, Almeida, Klick, Haythornthwaite, & Smith, 2008; Wolfe, Michaud, & Li, 2006), SCD research has also sough to understand the relationship between sleep and pain (Daniel et al., 2010; Graves & Jacob, 2014; Moscou-Jackson et al., 2015; Wallen et al., 2014). Specifically, three studies reported that increased sleep disturbance and parasomnias were significantly associated with increased pain frequency, pain severity, and SCD complications (Daniel et al., 2010; Moscou-Jackson et al., 2015; Wallen et al., 2014). One study however, found no significant differences in sleep scores based on pain intensity and severity (Graves & Jacob, 2014). Of the four total

studies, two were cross-sectional (Graves & Jacob, 2014; Wallen et al., 2014), one was longitudinal (Moscou-Jackson et al., 2015), and one was case-control (Daniel et al., 2010).

Many of the studies that evaluated the relationship between sleep and pain had limitations. One longitudinal study (*N*=75) conducted in adults with SCD included a measure of pain interference with no description of the measure's reliability and validity (Moscou-Jackson et al., 2015). Thus, it is unclear whether this measure was able to fully capture pain interference among adults with SCD. Additionally, the eligible sample included patients that were 1) treated with a stable pain management regimen, 2) free of infection, and 3) stable in terms of the management of their sickle cell disease (Moscou-Jackson et al., 2015). This strict inclusion criteria limits the generalizability of the findings and the confidence that these significant results would be found in a more diverse sample. While many of these studies highlighted a significant relationship between pain and sleep, sleep was not compared based on the presence of centralized pain. As discussed previously, evidence suggests that sleep disturbances co-occur with other centrally-mediated symptoms in patients with the following centralized pain conditions: chronic low back pain, TMD, and fibromyalgia (Heffner et al., 2011; Nicassio et al., 2002; Park & Chung, 2016). Further research is needed to support this relationship among patients with SCD that have centralized pain.

Psychological.

Depression.

There are multiple studies that have investigated the association of psychological influencing factors and pain in patients with SCD. Specifically, twelve studies have evaluated the association between depression and pain (Bakshi et al., 2018, 2017; Campbell et al., 2016; Carroll et al., 2016; Carroll et al., 2013; Ford, Grasso, Jones, Works, & Andemariam, 2017;

Jacob et al., 2015; Jerrell, Tripathi, & McIntyre, 2011; Lemanek et al., 2009; McClish et al., 2009; Sil et al., 2016; Wallen et al., 2014). Of the twelve studies, five were cohort (C. M. Campbell et al., 2016; C. P. Carroll et al., 2016a; Ford et al., 2017; Jerrell et al., 2011; McClish et al., 2009), five were cross-sectional (N Bakshi et al., 2018; P. C. Carroll et al., 2013; Eufemia Jacob et al., 2015; S Sil, Cohen, et al., 2016; Wallen et al., 2014), one was case-control (N Bakshi et al., 2017), and one was a randomized control trial (Lemanek et al., 2009). Seven studies support a positive association among depression, pain frequency, multifocal pain, lower heat pain thresholds, opioid use, and SCD-related complications (Bakshi et al., 2017; Carroll et al., 2016a; Jerrell et al., 2011; McClish et al., 2009; Sil et al., 2016; Wallen et al., 2014). One RCT found that patients receiving a massage intervention for 30 days had significantly less depression and pain intensity compared to controls (Lemanek et al., 2009).

Only half of the studies (*N*=6) evaluated differences in depression between patients with and without centralized pain (Bakshi et al., 2018; Campbell et al., 2016; Carroll et al., 2016; Ford et al., 2017; Jacob et al., 2015; Sil et al., 2016). Three of these studies were unable to detect any differences in depression based on the presence of centralized pain (Campbell et al., 2016; Ford et al., 2017; Jacob et al., 2015). These three studies, however, had very small samples (range, *N*=38-50) reducing the power to detect significant differences (Campbell et al., 2016; Ford et al., 2017; Jacob et al., 2015). There were additional limitations throughout the three studies that found no significant differences between patients with and without centralized pain (Campbell et al., 2016; Ford et al., 2017; Jacob et al., 2015). One cohort study divided patients based on a self-report of "the presence of moderate to severe pain on more than 50% of days in the last 6 months" (Ford et al., 2017). The use of a validated centralized pain PRO measure with strong psychometric properties (e.g., sensitivity, specificity) may been more appropriate to use within

this study and would increase the confidence in the findings. Overall, there is conflicting evidence regarding the relationship between depression and the incidence of centralized pain among patients with SCD. Further, study limitations including small sample sizes and a dichotomous self-reported centralized pain measure could have confounded the insignificant results. Ultimately, further research is needed to investigate whether there are significant associations between depression and centralized pain among those with SCD.

Anxiety.

There is a limited amount of evidence supporting a positive relationship between anxiety and pain among patients with SCD (Bakshi et al., 2018, 2017; Lemanek et al., 2009). Out of seven studies that have evaluated this relationship in patients with SCD (N Bakshi et al., 2018, 2017; Ford et al., 2017; Eufemia Jacob et al., 2015; Lemanek et al., 2009; Moody et al., 2017; Thomas et al., 2013), four found no significant associations between anxiety and pain (Ford et al., 2017; Jacob et al., 2015; Moody et al., 2017; Thomas et al., 2013). Three of the studies were RCTs including a yoga, massage, and healing touch with music intervention (Lemanek et al., 2009; Moody et al., 2017; Thomas et al., 2013). The limitations of these non-pharmacologic RCTs will be discussed in more detail within the following section; some examples of these limitations include a lack of blinding between intervention and control groups, small sample sizes, and no differentiation between those with and without centralized pain.

Two additional studies support significant associations among anxiety, centralized pain, and higher cold pain thresholds (Bakshi et al., 2018, 2017). However, one case-control study did not match cases and controls based on common confounders like age and sex, increasing the likelihood that differences between groups were influenced by these confounding variables and (Bakshi et al., 2017). Further, this study investigated the relationships among anxiety and several

other influencing factors including age, sex, depression, and catatrophization; however, no statistical corrections for multiple comparisons were made (Bakshi et al., 2017). Thus, there is an increased likelihood that the significant difference in anxiety among patients with SCD was found due to chance. Overall, the limitations of the studies described above highlight the need for more evidence to understand the relationship between anxiety and centralized pain in patients with SCD.

Catastrophizing.

The fourth psychological influencing factor included in this review is catastrophizing. Five studies have evaluated the relationship between catastrophizing and pain among patients with SCD (Bakshi et al., 2017; Campbell et al., 2016; Finan et al., 2018; Graves & Jacob, 2014; Sil et al., 2016). One cross-sectional study found that patients with pain had significantly higher catastrophizing scores (Sil et al., 2016). However, no significant differences in catastrophizing scores were found between those with chronic and episodic pain (Sil et al., 2016). Another cross-sectional study highlighted a significant negative correlation between worst pain severity and negative internalizing/catastrophizing in males (Graves & Jacob, 2014). Catastrophizing, however, was only measured using one item within the Pediatric Pain Coping Questionnaire. Additionally, this relationship was not found in females. One case-control study found that patients with increased catastrophizing had higher cold pain thresholds but lower mechanical pain thresholds (Bakshi et al., 2017). As discussed previously, this study did not match cases and controls or correct for multiple comparisons within their analysis. The last study that investigated the relationship between pain and catastrophizing utilized a longitudinal study design to evaluate the difference between those with high and low central sensitization determined via QST (Campbell et al., 2016). This study found no significant differences in catastrophizing between

the two groups, however, it was the only study to differentiate patients with and without centralized pain based on objective testing. Overall, there is conflicting evidence regarding the relationship between catastrophizing and pain among patients with SCD. Further, only two studies (C. M. Campbell et al., 2016; Patrick H Finan et al., 2018) evaluated the relationship between catastrophizing and pain using a predictive study design. Due to these reasons and the limitations of the studies described above, further research is needed to evaluate the relationship between catastrophizing and pain in patients with SCD.

Pain control beliefs.

The psychological variable, pain control beliefs, has been identified as an important factor that can influence how a patient processes and treats pain (Higgins et al., 2015; Oliveira et al., 2009; Spinhoven et al., 2004). However, no studies, within the past ten years, have explored the relationship pain control beliefs and pain among patients with SCD.

Situational.

Sickle cell stigma.

Situational factors also have the ability to influence pain. Multiple research studies have identified stigmatization in SCD manifested by racial biases and altered perceptions of opioid use and addiction (Zempsky, 2009). It is hypothesized that since a larger percentage of patients with SCD are ethnic minorities, they are faced with stigmatization. Further, research evidence suggests that ethnic minorities are frequently undertreated for pain compared to non-Hispanic whites (Green & Hart-Johnson, 2010). Contrary to minimal addiction and opioid overdose rates, evidence suggests clinicians often perceive that patients with SCD are at an increased risk for opioid abuse, misuse, and addiction (Zempsky, 2009). Only two cross-sectional articles have evaluated the relationship between sickle cell stigma and pain (Bediako et al., 2016; Martin et

al., 2018). One study supports a significant positive relationship between perceived stigma and increased pain interference (Martin et al., 2018). The findings of this study also support a significant negative relationship between increased perceived stigma and pain reduction during admission for VOC (Martin et al., 2018). The second study highlighted that sickle cell stigma factors including social exclusion, internalized stigma, and expected discrimination were significantly associated with acute care visits for SCD pain (Bediako et al., 2016). This study, however, utilized self-reported measures for health service use and hospitalizations which may be subject to recall bias. Further, this study did not evaluate the effects of potential confounding variables, for example anxiety, depression, and opioid use. Overall, there are potential risks of bias within the studies that evaluated the relationship between sickle cell stigma and pain. Further research is needed to support the evidence that sickle cell stigma is associated with pain in patients with SCD.

Trauma exposure.

Another situational variable that has been shown to influence pain is trauma exposure (Hauser, Kosseva, Uceyler, Klose, & Sommer, 2011; Kanzawa-Lee et al., 2018; Oram et al., 2012; Phillips & Clauw, 2011; Schofferman, Anderson, Hines, Smith, & Keane, 1993; Spiegel et al., 2015). Only two studies evaluated the relationship between trauma exposure and pain in patients with SCD (P. C. Carroll et al., 2013; Ford et al., 2017). One cross-sectional study highlighted that there were no significant differences in health service utilization based on trauma exposure (Carroll et al., 2013). This study included all health service visits within their analyses, not solely those for pain. Many health service utilization visits are unlikely to be associated with trauma exposure (e.g., infection) and would have reduced the ability to detect a significant difference. One longitudinal cohort study, however, found significant differences in

self-reported chronic pain in those that were exposed to interpersonal violence compared to those unexposed (Ford et al., 2017). While controlling for age and depression, those who were exposed to interpersonal violence were nearly five times more likely to report chronic pain (Ford et al., 2017). However, as discussed previously, this study utilized a dichotomous measure for centralized pain. The lack of a continuous measure for centralized pain may have threatened the statistical validity and confounded these findings. In summary, internal and statistical conclusion validity threats may have confounded the findings within the few studies that have evaluated the relationship between trauma exposure and pain. Further research is needed to support this relationship among patients with SCD.

Social support.

The last situational variable included in this review is social support (Lopez-Martinez et al., 2008; Montoya et al., 2004; Smite et al., 2012). Only one cross-sectional study has evaluated this relationship (Carroll et al., 2013). As described above, this study found no significant associations between health service utilization and pain. This study included all health service visits within their analyses which could have impacted the insignificant results. Further, this study did not distinguish patients with and without centralized pain so it is unclear whether the relationship between pain and social support would be significant within only those experiencing centralized pain.

Cognitive.

Cognitive function.

As discussed in the previous section, there is a paucity of research that has evaluated the relationship between cognitive function and pain among patients with centralized pain. Further. no studies have analyzed the relationship between cognitive function and pain among patients

with SCD. Further research is needed to support the significant relationship between this centrally-mediated symptom and pain within this population.

This section provides a comprehensive synthesis of the literature that has investigated the association between several physiological, psychological, situational, and cognitive factors and pain among patients with SCD. These factors included genetics, sex, age, sleep, fatigue, depression, anxiety, catastrophizing, pain control beliefs, sickle cell stigma, trauma exposure, social support. The predictive factors included within the proposed study were selected based on the gaps identified within the literature presented above. Although many studies evaluated the association among several variables and pain, no studies accounted for all centrally-mediated symptoms included within the S.P.A.C.E. symptom cluster. Only two out of the 26 studies included more than one construct within the S.P.A.C.E. symptom cluster within their research designs (i.e., sleep and depression) (C. M. Campbell et al., 2016; Wallen et al., 2014). Empirical evidence suggests that a majority of patients with centralized pain present with more than one centrally-mediated symptom (Davis et al., 2017). Including only one or two centrally-mediated symptom when evaluating associations with pain does not capture this multisymptomatic presentation and may not account for individual variability within the sample. This is a major gap identified within the literature that informed the inclusion of all the variables within the S.P.A.C.E. symptom cluster (i.e., sleep impairment, widespread pain, anxiety, depression, cognitive function, fatigue) in the proposed study.

Although several of the factors discussed require further investigation (e.g., sickle cell stigma, trauma exposure, social support), their relationships with opioid consumption and pain

interference will not be explored in the proposed study due to sample size limitations. The number of potentially eligible adolescents and young adults ages 14-35 years with SCD treated at the Michigan Medicine and Mott Children's Hospital Comprehensive Sickle Cell Clinics is insufficient to provide adequate power to detect relationships among all 12 factors described above and pain outcomes. Further, the completion of 12 different patient-reported outcome survey measures that capture all these factors would pose significant participant burden. For these reasons, the proposed aims of this study will focus on the significant gaps found regarding centralized pain, pain catastrophizing, and centrally-mediated symptoms included within the S.P.A.C.E. symptom cluster. Further, these eight variables address several of the core components within the Theory of Unpleasant Symptoms which has guided this study—physiologic factors (centralized pain, sleep, and fatigue), psychologic factors (depression, anxiety, and pain catastrophizing), symptoms (widespread pain), and impact (cognitive function).

As discussed previously, the gaps identified within the section above highlight a lack of understanding regarding the daily impact of several co-occurring influencing factors on pain. Limited understanding of the co-occurring factors that influence pain could impact the way pain is managed within this population and could explain the lack of effective pharmacologic and nonpharmacologic therapies available for patients with SCD. In order to improve pain management within this population, it is imperative to understand why the current treatments utilized among patients with SCD are ineffective in reducing the daily impact of pain within this population. The following section will discuss therapies available to treat pain among patients with SCD and evaluate the current evidence regarding SCD-related pain management.

SCD-related Pain Management

There are a variety of therapeutic options available to treat pain among patients with SCD. These treatments include opioids, adjuvants, and disease modifying agents that indirectly affect pain. Although many of these treatments are employed within this population, one prospective cohort study identified that many patients still report frequent daily pain (Smith, Penberthy, Bovbjerg, Mcclish, & Roberts, 2008). Further, evidence suggests that almost one-third of patients with SCD experience pain almost every day (Smith et al., 2008). The following section will outline the Clinical Practice Guidelines and RCTs that are used to treat pain in those with SCD. Further, this section will identify specific gaps within the current evidence that may contribute to inadequate pain management and the pervasive problem of pain within this population.

As discussed previously, VOC is the most common complication of SCD. VOCs often require hospitalizations to manage severe pain and to reduce the likelihood of further complications. For this reason, many of the treatments available for SCD-related pain focus on acute pain. Clinical practice guidelines published by the National Heart Lung and Blood Institute (2014) support the rapid initiation of analgesics, opioids and nonopioids, when patients present with VOC. Further, in those that present with severe pain, the initiation of parenteral opioids is strongly recommended (National Heart, Lung, and Blood Institute, 2014). Although opioids are indicated for acute VOC, evidence suggests that they are ineffective in treating the variety of pathophysiologic mechanisms that contribute to centralized pain (Brummett et al., 2013; Corli et al., 2017; Finan et al., 2018; Hanks & Forbes, 1997; Janda et al., 2015; Phillips & Clauw, 2011; Wasserman, Brummett, Goesling, Tsodikov, & Hassett, 2014). Despite this, many patients with SCD continue to take opioids every day (Finan et al., 2018). Although the Clinical Practice Guidelines for SCD-related pain management focus on the use of analgesics including opioids

and non-steroidal anti-inflammatory drugs (NSAIDs), several RCTs have been conducted to evaluate the effectiveness of a variety of non-opioid analgesics and disease modifying therapies to reduce pain in this population.

Non-opioid analgesics.

One pilot RCT compared the effectiveness of pregabalin to reduce pain and improve function compared to a placebo in adults with SCD (*N*=22) (Schlaeger et al., 2017). Pregabalin affects voltage-gated calcium channels to decrease central sensitization and nociceptive transmission and is used to treat neuropathic pain (Schlaeger et al., 2017). Patients were included in the study if they had a history uncontrolled pain with a current pain score of ≥ 4. Participants received pregabalin 75mg twice daily for three months. Doses could be titrated up as needed to a maximum of 600mg daily. This RCT reported no significant differences between groups on neuropathic pain, pain severity, and composite pain index (Schlaeger et al., 2017).

This pilot RCT had many limitations. First, six participants out of the total sample did not complete the trial, further reducing the sample and the power to detect differences between groups. Additionally, participants in the pregabalin and control group differed on all pain scores at baseline including average pain index (3.8 vs. 4.8), composite pain index (36.1 vs. 46.5), Neuropathic Pain Symptom Index (29.6 vs. 44.5), and Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) scores (8.0 vs. 9.5). These differences between groups indicate that the placebo group had increased pain severity and neuropathic pain at baseline compared to the treatment group. Thus, it is likely that large group differences in pain influenced the results found between groups. Further, many of the participants did not have neuropathic signs and symptoms at the start of the trial. Scores ≥12 on the S-LANSS is indicative of neuropathic pain (Bennett, Smith, Torrance, & Potter, 2005). As reported previously, baseline scores for the

placebo and treatment groups were 9.5 and 8.0. Therefore, many patients were not experiencing neuropathic pain and would not have benefited from the initiation of pregabalin. Overall, results of this study may have been more significant if only patients with signs and symptoms of neuropathic pain were included and stratified between groups based on baseline pain scores.

Disease modifying therapies.

Several studies have investigated the benefits of disease modifying therapies to reduce VOC, hospitalizations, and pain intensity in patients with SCD (Ataga et al., 2017; Brousseau et al., 2015; Charache et al., 1995; Gladwin et al., 2011; Ferster et al., 1996; Heeney et al., 2016; Morris et al., 2013; Niihara et al., 2018; Wang et al., 2011; Wun et al., 2013). First, evidence supports the daily use of hydroxyurea, or hydroxycarbamide, in children and adults who experience three or more VOCs with severe pain per year (Charache et al., 1995; Ferster et al., 1996; National Heart, Lung, and Blood Institute, 2014; Wang et al., 2011). Hydroxyurea is a myelosuppressive agent that increases fetal hemoglobin (HbF) levels, decreases circulating leukocytes and reticulocytes, and increases RBC volume (National Heart, Lung, and Blood Institute, 2014). One RCT (N=299) that has greatly influenced current clinical practice recommendations identified that hydroxyurea therapy reduced the incidence of VOC (2.5 vs. 4.5 per year; $p \leq 0.001$). Further, fewer patients taking hydroxyurea had acute chest syndrome (25 vs. 51 patients; $p \leq ,0.001$) and underwent transfusions (48 vs. 73; p=0.001)(Charache et al., 1995). Those taking hydroxyurea also had significantly longer time to first (3 vs. 1.5 months; p=0.01) and second (8.8 vs. 4.6 months; $p \leq 0.001$) VOC compared to the placebo group. Two additional RCTs also support the use of hydroxyurea in children (Ferster et al., 1996; Wang et al., 2011). One RCT (N=22) identified that patients taking hydroxyurea had less hospitalizations (p=0.0016) and less days in the hospital (p=0.0027) compared to those taking placebo (Ferster et al., 1996).

The other RCT (*N*=193) identified that those taking hydroxyurea had significantly less pain events (63 vs. 121; *p*=0.004) than those taking placebo (Wang et al., 2011).

While these hydroxyurea RCTs had positive effects regarding VOC frequency, hospitalization rates, and length of hospital stay, they did not assess the effect of hydroxyurea on pain severity. Thus, it is unclear whether hydroxyurea is effective in reducing daily pain severity among those with SCD. Further, these studies did not differentiate those with and without centralized pain in their sample. While hydroxyurea was effective in reducing acute pain outcomes in some patients, it may not have been beneficial in those with centralized pain. One of the RCTs excluded patients who consistently took more than 30 capsules of oxycodone over two weeks (Charache et al., 1995). Thus, it is possible that many patients with centralized pain prescribed daily opioids were excluded from this study making it unclear if hydroxyurea would have positive effects among those with centralized pain. Lastly, these three RCTs did not assess the variety of centrally-mediated factors (e.g., sleep, cognition, depression, anxiety, catastrophizing) that are known to influence pain. Since these factors were not measured and/or controlled for, it is unclear whether confounding variables influenced the positive findings within these samples.

Evidence supports the effectiveness of two amino acid therapies, L-glutamine and L-arginine, in reducing pain among patients with SCD (Morris et al., 2013; Niihara et al., 2018). Evidence suggests that patients with SCD have decreased availability of the amino acid, arginine, which may disrupt many cellular and organ functions (Bakshi & Morris, 2016). One RCT (*N*=38) found that patients taking L-arginine during hospitalization for VOC had a significant reduction in parenteral opioid use (1.9±2.0 mg/kg vs. 4.1±4.1mg/kg; *p*=0.02) and lower pain intensity (1.9±2.4 vs. 3.9±2.9; *p*=0.01) at discharge compared to placebo (Morris et

al., 2013). There were no significant differences, however, in hospital length of stay between groups (Morris et al., 2013). The second amino acid, L-glutamine, increases the flexibility of RBCs and improves oxygen transport within the blood (Niihara et al., 2018). One RCT (*N*=230) found that those taking L-glutamine daily for 48 weeks had fewer VOCs (3.0 vs. 4.0; *p*=0005) and hospitalizations (2.0 vs. 3.0; *p*=0.005) than those taking placebo (Niihara et al., 2018).

Although these two amino acid RCTs revealed positive effects among a subset of patients with SCD, it is unclear if these effects would have been reported in a more diverse sample. The L-arginine trial excluded patients that may have had more severe and/or centralized pain (Morris et al., 2013). Two exclusion criteria within this study were 1) patients that had more than 10 hospitalizations per year, and 2) those who had a history of opioid dependence (Morris et al., 2013). The authors did not describe how opioid dependence was identified; thus, it is possible that patients with centralized pain who are prescribed daily opioids were excluded from the study. The inclusion of these patients could have significantly reduced the positive effects found among those receiving L-arginine. Further, the study period ended at discharge so it is unclear if the drug would have positive effects on daily pain severity post-VOC hospitalization (Morris et al., 2013). The RCT of L-glutamine versus placebo also did not differentiate those with and without centralized pain (Niihara et al., 2018). Further, this study only assessed outcomes related to VOC frequency and acute care utilization rates within the 48-week study period, making it unclear whether L-glutamine is effective in reducing daily pain severity (Niihara et al., 2018). Lastly, neither of these RCTs controlled for potential centrally-mediated pain influencing factors (Morris et al., 2013; Niihara et al., 2018). Overall, the evidence does not provide support for the use of amino acid therapy to reduce pain in patients with SCD that have centralized pain and co-occurring centrally-mediated symptoms.

One RCT supports the use of a monoclonal antibody, crizanlizumab, among adolescents and adults with SCD that have two or more VOC per year (Ataga et al., 2017). Crizanlizumab binds to P-selectin, which contributes to the adhesion of sickled RBCs within blood vessel walls. Inhibiting P-selectin with crizanlizumab prevents vaso-occlusion, inflammation, and pain (Ataga et al., 2017). The RCT (*N*=193) compared the effectiveness of high-dose crizanlizumab, low-dose crizanlizumab, and placebo and found that those who received 14 doses of high-dose crizanlizumab over 52 weeks had significantly less VOCs (1.63 vs. 2.98; *p*=0.01), less uncomplicated VOCs (1.08 vs. 2.91; *p*=0.02), and longer time to first (4.07 vs. 1.38 months; *p*=0.001) and second (10.32 vs. 5.09 months; *p*=0.02) VOC compared to placebo (Ataga et al., 2017). There were no significant differences in pain severity and pain interference, assessed via the Brief Pain Inventory, between groups. While this RCT supports the effectiveness of crizanlizumab to reduce VOC rates and increase the time to VOCs, no effects were found on daily pain severity and interference. Thus, patients would still need additional interventions if they are experiencing daily pain. While the investigators compared the differences in outcomes based on sex, SCD genotype, and number of VOCs in the previous year, they did not evaluate outcomes between those with and without centralized pain. Thus, it is unclear if crizanlizumab would be effective within this population. Lastly, this study did not assess the effect of confounding pain influencing factors that could influence the positive findings. Specifically, the presence and/or absence of several centrally-mediated symptoms (e.g., sleep, cognition, depression) could have differed among the treatment and placebo groups and may have influenced the results.

Four RCTs evaluated the effectiveness of three additional therapies in reducing pain, prasugrel, intravenous (IV) magnesium, and inhaled nitric oxide (NO) (Brousseau et al., 2015;

Gladwin et al., 2011; Heeney et al., 2016; Wun et al., 2013). None of these studies found significant differences in pain between the treatment and placebo groups (Brousseau et al., 2015; Gladwin et al., 2011; Heeney et al., 2016; Wun et al., 2013). Limitations in assay sensitivity may explain the negative findings of these four RCTs. Assay sensitivity is defined as the ability to distinguish an effective intervention from a less effective or ineffective intervention (Dworkin et al., 2012). A detailed evaluation of these studies' limitations, including limitations in assay sensitivity, will be delineated in the following paragraphs.

Two of the RCTs evaluated the effectiveness a blood cell modifying therapy, prasugrel, in reducing pain in patients with SCD (Heeney et al., 2016; Wun et al., 2013). Prasugrel, an anti-platelet medication, reduces the formation of blood clots. First, one RCT conducted in children and adolescents (*N*=341) showed that the rate of VOC, hospitalization, and analgesic use was not significantly different between the prasugrel and placebo groups (Heeney et al., 2016). Further, there were no significant differences in daily pain severity, measured via the FACES pain scale, between the two groups (Heeney et al., 2016). The second RCT (*N*=62) evaluated the efficacy of prasugrel to reduce pain in adults with SCD (Wun et al., 2013). This study found no significant differences in pain frequency and severity between groups (Wun et al., 2013).

Inhaled NO has been shown to ameliorate several adverse effects of VOC, for example vasoconstriction and platelet aggregation (Gladwin et al., 2011). One RCT studied whether inhaled NO gas would reduce VOC duration in patients presenting to the Emergency Department or hospital unit (*N*=150)(Gladwin et al., 2011). This study found no significant differences between those that received inhaled NO for up to 72 hours and those that received inhaled nitrogen placebo based on the following outcomes: time to VOC resolution, length of hospitalization, pain severity scores over time, and total dose of opioids (Gladwin et al., 2011).

Lastly, it is hypothesized that IV magnesium has the potential to benefit those experiencing VOC due to its anti-inflammatory and vasodilation effects (Brousseau et al., 2015). One RCT evaluated the effectiveness of IV magnesium to reduce length of stay and opioid use in children, adolescents, and young adults with SCD (*N*=204) (Brousseau et al., 2015). This study found no significant differences in hospital length of stay and opioid use between those receiving IV magnesium versus placebo (Brousseau et al., 2015).

The four RCTs that evaluated the effectiveness of prasugrel, inhaled NO, and IV magnesium on pain did not have significant findings (Brousseau et al., 2015; Gladwin et al., 2011; Heeney et al., 2016; Wun et al., 2013). It is possible that none of these treatments are effective in reducing pain among patients with SCD; however, limitations in assay sensitivity could have also influenced the results. Patients within one of the prasugrel RCTs had low pain intensity scores at baseline within the prasugrel and placebo groups (1.8 vs. 2.4), highlighting potential limitations in assay sensitivity (Wun et al., 2013). The prasugrel RCT could have improved assay sensitivity by limiting inclusion to patients with baseline pain ≥ 4 (on a numeric rating scale ranging from 0-10), since patients with greater pain are more likely to benefit from pharmacologic treatment (Dworkin et al., 2012). The second prasugrel RCT also has limitations in assay sensitivity based on patient factors (Gladwin et al., 2011). This RCT reported significant differences in patient characteristics between study sites—two of sites enrolled patients with less pain, shorter hospitalization times, and less cumulative opioid dose (Gladwin et al., 2011). These patient differences may have threatened the internal validity of the study and confounded the findings.

Overall, evidence supports the efficacy of the following four non-opioid therapies in reducing pain in SCD: hydroxyurea, L-arginine, L-glutamine, and crizanlizumab (Charache et

al., 1995; Ferster et al., 1996; Morris et al., 2013; National Heart, Lung, and Blood Institute, 2014; Niihara et al., 2018; Wang et al., 2011). As discussed previously, although these drugs are effective within these trials, it is unclear whether they are effective in reducing daily pain severity among those with centralized pain. Further, since no centrally-mediated factors were evaluated within these RCTs, it is unclear whether the presence or absence of these variables would have influenced the effects found on pain.

Non-pharmacologic therapies.

Within the past ten years, six non-pharmacologic RCTs have been conducted among patients with SCD to reduce the incidence of pain (L P Barakat, Schwartz, Salamon, & Radcliffe, 2010; Miriam O. Ezenwa et al., 2016; Moody et al., 2017; Schatz et al., 2015; Thomas et al., 2013). Four of these studies demonstrated positive intervention effects; however, these effects were minimal (Ezenwa et al., 2016; Moody et al., 2017; Schatz et al., 2015; Thomas, Stephenson, Swanson, Jesse, & Brown, 2013).

One RCT conducted among patients hospitalized for VOC (N=73) compared effects between a yoga intervention group and an attention control group on pain, anxiety, length of stay, and opioid use (Moody et al., 2017). Participants with a pain score of $\geq$7 at admission were randomized to the yoga or control group. The yoga intervention included four segments that focused on mindfulness, asanas (practicing different body positions with awareness of breath), breathing exercises, and guided relaxation (Moody et al., 2017). Those in the control group were provided with 30-minute sessions in which the yoga instructor played a nature sounds CD. Within the control group, the yoga instructor was available to stay with participants for 30 minutes, but no exercises were taught. Participants in the yoga group experienced greater reduction in mean pain severity (-0.6±0.96 vs. 0.0±1.37; p=0.029) after the first yoga session

compared to the control group (Moody et al., 2017). However, no differences were found after subsequent sessions (Moody et al., 2017). Further, there were no significant differences between groups in total IV opioid use during hospitalization.

The intervention described above has several limitations. First, participants and interventionists were not blinded to the treatment, increasing the likelihood that patients randomized to the control arm expected no reduction in pain, which could have subsequently influenced the findings. Further, evidence suggests that yoga interventions are beneficial in reducing pain among those with centralized pain (Büssing, Ostermann, Lüdtke, & Michalsen, 2012; Tekur, Nagarathna, Chametcha, Hankey, & Nagendra, 2012; Williams et al., 2005). The RCT described above, however, was conducted within an inpatient setting while patients were experiencing an acute VOC with severe pain (Moody et al., 2017). Further, this study did not differentiate those with and without centralized pain. Thus, the insignificant results could be due to the fact that participants were not experiencing centralized pain and, therefore, an intervention targeting central pain mechanisms would be ineffective.

The second nonpharmacologic RCT conducted among children and adolescents with SCD (N=46) evaluated the effectiveness of a Cognitive Behavioral Therapy (CBT) intervention on pain, coping, negative thinking, and activity (Schatz et al., 2015). Participants in the CBT group received CBT training by a licensed clinical psychologist and were given a smartphone that included a CBT skills program facilitating deep breathing, progressive muscle relaxation, and guided imagery (Schatz et al., 2015). CBT skill use was recorded by the smartphone when a participant opened the skills program. This study found that smartphone-recorded CBT skill use significantly predicted next-day pain intensity (x^2[12]= 3.91; p=0.048) (Schatz et al., 2015).

Although this study had positive results, there were group differences at baseline that could have influenced the results. Patients within the intervention group had more pain episodes that resulted in inpatient admissions and/or ER visits during the previous year than the control group (3.8 vs. 5.4) (Schatz et al., 2015). Although this difference was not statistically significant, those in the intervention group may have been more willing to participate with CBT skills because they had greater pain severity. Another limitation of this RCT is a lack of participant blinding. Specifically, those receiving the intervention may have expected their pain to decrease during the study period, which could subsequently explain the significant difference in pain severity scores between groups. Further, this RCT did not distinguish between those with and without centralized pain. Since CBT interventions target central pain mechanisms, it could be hypothesized that those with centralized pain would experience the most benefit from practicing CBT skills. Thus, the differences between groups may have been more significant if this study included only those with centralized pain. Lastly, although this study analyzed the effect of the intervention on coping, negative thinking, and activity, it did not control for any other centrally-mediated pain influencing factors (e.g., sleep, cognition, depression, anxiety) that could have influenced the positive findings.

The third non-pharmacologic RCT conducted among adults with SCD (*N*=27) compared an audio-visual relaxation intervention to an attention control group (Miriam O. Ezenwa et al., 2016). Those in the intervention group received one 12-minute guided relaxation clip at baseline and six additional video clips (2-20 minutes in length) with similar content on a tablet device. Participants were instructed to watch at least one video daily but were encouraged to watch a video at stress onset and whenever desired. The attention control group participated in a 12-minute computer-based discussion regarding their SCD experience at baseline. The control group

also recorded daily stress and pain scores for the duration of the study period. All patients and most study personnel were blinded to group assignments. Participants in the intervention group had significantly lower pain scores after the baseline intervention (4.1 vs. 6.3; 95% CI [-3.343, -0.364]) as well as significant lower composite pain index scores after the two-week study period (35 vs. 41.8; 95% CI [-17.872, -0.406]) compared to the control group (Ezenwa et al., 2016). However, there were no significant differences in opioid use between groups (Ezenwa et al., 2016). Also, similarly to the previous two nonpharmacologic RCTs presented, this study did not distinguish those with and without centralized pain. Thus, it is unclear if this intervention would be effective in reducing pain among those with central pain mechanisms.

The fourth non-pharmacologic RCT conducted among adults hospitalized for VOC (N=17) compared a healing touch with music intervention to an attention control with music group (Thomas, Stephenson, Swanson, Jesse, & Brown, 2013). This RCT evaluated the effectiveness of the intervention to reduce anxiety, stress, pain, and analgesic use. The intervention included four healing touch sessions that were administered for 30 minutes over four consecutive days (Thomas et al., 2013). Those in the control group received four 30-minutes sessions that included only music (Thomas et al., 2013). There were no significant differences found in daily pain between groups except for on Day 4; those in the attention control group had significant reductions in present pain post-intervention on Day 4 (4.55 vs. 7.17; p=0.03) compared to the intervention group. Further, this study found that those in the intervention group had a larger mean change in pain score from pre- to post-intervention on Day 1 (1.67 vs. 0.92; p<0.01) compared to the control group. No subsequent differences were found between groups (Thomas et al., 2013).

Several limitations of this pilot RCT could have influenced the findings. First, this study was not powered to detect these differences between groups due to the small sample (*N*=17) (Thomas, Stephenson, Swanson, Jesse, & Brown, 2013). Participants and study personnel were not blinded to the intervention. Thus, participants randomized to the intervention group may have expected differences in outcomes following the healing touch with music intervention. The authors of this study reported that the inpatient setting was not conducive to the intervention since there were several interruptions during the intervention and control sessions (Thomas et al., 2013). These interruptions could have limited the effectiveness of the healing touch with music intervention on reducing pain. Similar to the yoga RCT conducted by Moody et al. (2017), this RCT was conducted among those hospitalized with VOC and there was no distinction between those with and without centralized pain. Thus, it is unclear whether this intervention can reduce pain via targeting central pain mechanisms like yoga, exercise, and distraction.

The fifth nonpharmacologic RCT conducted among those with SCD included a massage therapy intervention (Lemanek et al., 2009). Children and their primary caregiver (*N*=34) were randomized to a massage therapy or attention control group (Lemanek et al., 2009). A massage therapist visited those within the intervention group at home weekly for four weeks. Further, caregivers, trained on proper massage techniques, were asked to give their child massages between therapist days (Lemanek et al., 2009). Those in the attention control group were visited weekly at home by a research assistant to collect outcome measure forms (Lemanek et al., 2009). Children within the study rated their levels of pain each morning and evening. Depression measures were given at baseline and study completion while measures of anxiety were given weekly (Lemanek et al., 2009). After the 30-day study period, participants in the intervention group had significantly less depression (45 vs. 46.7; p=0.05), anxiety (40.1 vs. 43.9; p=0.01), and

pain ratings (F=4.11; p=0.05) compared to the control group, highlighting potential mediating effects of depression and anxiety on pain. There were no significant differences between groups based on health care utilization (Lemanek et al., 2009).

Although this massage RCT found positive effects, there were limitations within the study design. First, participants and study personnel were not blinded, so it is possible that participants randomized to the intervention group may have expected differences in outcomes following the massage intervention. Similarly, those in the attention control group would not expect differences in pain and psychological outcomes since they were not receiving the intervention. The authors of this study reported that it is likely this intervention was not standardized between participants since caregivers were required to give the massage to their children on days the therapist did not come (Lemanek et al., 2009). Similar to the other RCTs described above, this study did not distinguish patients with and without centralized pain. Thus, it is unclear if this intervention would be effective if it was conducted in only those with centralized pain.

The last RCT, conducted among children and adolescents with SCD (N=53), investigated the effectiveness of a cognitive behavioral pain management intervention compared to a disease education intervention on pain and coping, school attendance, and health-related hindrance (Barakat, Schwartz, Salamon, & Radcliffe, 2010). Participants and a family support person were randomized to receive a brief pain intervention or a disease education attention control intervention at home. The intervention and control sessions consisted of four 90-minute sessions that each included a discussion of SCD and disease management. The cognitive behavioral pain management intervention consisted of deep breathing/relaxation, coping, and guided imagery while the disease education intervention included communication about disease, management,

and health issues. This RCT found no significant differences between groups among all pain, psychosocial, and health-related variables (Barakat, Schwartz, Salamon, & Radcliffe, 2010).

Gaps

In summary, the previous section provided a thorough review of the literature published within the last 10 years that has analyzed the relationships among various physiological, psychological, situational, and cognitive factors and SCD-related pain. Factors described above include genetics, sex, age, sleep, fatigue, depression, anxiety, catastrophizing, pain control beliefs, sickle cell stigma, trauma exposure, social support. Several gaps and limitations within the literature have been identified. A comprehensive summary of these gaps and the variables selected within the proposed study was provided following the 'pain-influencing factors in patients with SCD' section.

Several gaps among pain management RCTs were discussed within the previous section. First, the majority of the pharmacologic RCTs have focused on reducing nociceptive pain and acute vaso-occlusive crises among patients with SCD. However, recent evidence suggests that central sensitization and centralized pain manifestations (e.g., widespread pain) are present within a subset of patients with SCD (Brandow et al., 2015; Brandow et al., 2013; Carroll et al., 2016; Ezenwa et al., 2015; O'Leary et al., 2013; Schaibl & Richter, 2004; Zempsky et al., 2017). These findings may support the initiation of non-opioid and nonpharmacologic therapies that are known to be effective among other centralized pain populations. Despite evidence supporting the implementation of nonpharmacologic interventions among patients with SCD, several of the non-opioid and non-pharmacologic RCTs were ineffective or had minimal positive findings.

As discussed above, it is unclear whether the minimal effects found within the non-opioid and non-pharmacologic RCTs are due to the fact that these RCTs were conducted in patients

experiencing nociceptive, rather than centralized, pain. Prior to further intervention research, it is necessary to understand the pain presentation unique to those with SCD. For this reason, we will evaluate the incidence and severity of centralized pain, pain catastrophizing, and centrally mediated symptoms via reliable and validated patient-reported outcome (PRO) measures. We will also evaluate the predictive relationships among these factors and opioid consumption. Table 1 delineates specific approaches within the proposed dissertation project used to address many of the gaps discussed.

Table 1

Summary of Identified Gaps in the Literature and Plans for Addressing the Gaps in the Proposed Project

Gaps in the Literature	Addressing Gaps in the Literature
1. No studies among patients with SCD have evaluated the impact of all centrally-mediated variables within the S.P.A.C.E. symptom cluster that are known to co-occur with centralized pain (Shattuck & Muehlenbein, 2016; Williams, 2018).	I will describe the incidence and severity of all six S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, affective perturbation [anxiety and depression], cognitive function, and energy deficit [fatigue]), among adolescents and young adults with SCD (Aim 1). I will use two-part predictive models to evaluate the predictive relationships among S.P.A.C.E. symptoms, opioid consumption, and pain interference one month post-baseline in adolescents and young adults with SCD (Aim 2). Lastly, I will characterize the co-occurrence of individual baseline S.P.A.C.E. symptoms, pain interference, average daily opioid consumption, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) measured via the body map within the GeoPain @ Home smartphone application in adolescents and young adults with SCD via bivariate correlation analyses (Aim 4).

2. Approximately 50% of the studies that have evaluated the various pain-influencing factors among patients with SCD did not distinguish patients with and without centralized pain.	The ACR 2011 Fibroymaylgia survey criteria will be used to measure centralized pain. The published literature provides evidence of the measure's internal consistency reliability, sensitivity, specificity, responsiveness, and content and convergent validity (Häuser et al., 2012; Neville et al., 2018; Wolfe et al., 2016, 2011; Wolfe, Walitt, Rasker, Katz, & Häuser, 2015). I will describe the incidence and severity of centralized pain among adolescents and young adults with SCD (Aim 1). I will use two-part predictive models to evaluate the predictive relationships among centralized pain, opioid consumption, and pain interference one month post-baseline in adolescents and young adults with SCD (Aim 3).
3. There is conflicting evidence regarding the predictive relationship between pain catastrophizing and pain among those with SCD.	I will describe the incidence and severity of pain catastrophizing among adolescents and young adults with SCD (Aim 1). I will use two-part predictive models to evaluate the predictive relationships among pain catastrophizing, opioid consumption, and pain interference one month post-baseline in adolescents and young adults with SCD (Aim 3).

References

Adams, P., Kirzinger, W., & Martinez, M. (2013). Summary Health Statistics for the U.S. Population: National Health Interview Survey , 2012. *Vital Health Stat*, *10*(259).

Aicher, S. A., Hermes, S. M., Whittier, K. L., & Hegarty, D. M. (2012). Descending projections from the rostral ventromedial medulla (RVM) to trigeminal and spinal dorsal horns are morphologically and neurochemically distinct. *Journal of Chemical Neuroanatomy*, *43*(2), 103–111. https://doi.org/10.1038/jid.2014.371

Albe-Fessard, D., Berkley, K. J., Kruger, L., Ralston, H. J. 3rd, & Willis, W. D. J. (1985). Diencephalic mechanisms of pain sensation. *Brain Research*, *356*(3), 217–296.

Allen, K. D., Renner, J. B., Devellis, B., Helmick, C. G., & Jordan, J. M. (2008). Osteoarthritis and sleep: the Johnston County Osteoarthritis Project. *The Journal of Rheumatology*, *35*(6), 1102–1107. https://doi.org/10.1007/978-1-4614-5915-6

Alves, J. M., & Lin, K. (2018). Neuropathic Pain: A Review of Interneuronal Disinhibition. *Archives of Neuroscience*, *5*(1), 1–7. https://doi.org/10.5812/archneurosci.12290.Review

Ameringer, S., Elswick Jr, R. K., & Smith, W. (2014). Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing*, *31*(1), 6–17. https://doi.org/10.1177/1043454213514632 [doi]

Andersen, K. G., Aasvang, E. K., Kroman, N., & Kehlet, H. (2014). Intercostobrachial nerve handling and pain after axillary lymph node dissection for breast cancer. *Acta Anaesthesiologica Scandinavica*, *58*(10), 1240–1248. https://doi.org/10.1111/aas.12393

Andersen, S., & Skorpen, F. (2009). Variation in the COMT gene: Implications for pain perception and pain treatment. *Pharmacogenomics*, *10*(4), 669–684. https://doi.org/10.2217/pgs.09.13

Antunes, F. D., Propheta, V. G. S., Vasconcelos, H. A., & Cipolotti, R. (2017). Neuropathic pain in patients with sickle cell disease: a cross-sectional study assessing teens and young adults. *Annals of Hematology*. https://doi.org/10.1007/s00277-017-2984-z

Ataga, K. I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., … Rother, R. P. (2017). Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *New England Journal of Medicine*, *376*(5), 429–439. https://doi.org/10.1056/NEJMoa1611770

Bakshi, N, Lukombo, I., Belfer, I., & Krishnamurti, L. (2018). Pain catastrophizing is associated with poorer health-related quality of life in pediatric patients with sickle cell disease. *Journal of Pain Research*, 947–953.

Bakshi, N, Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Bakshi, Nitya, & Morris, C. (2016). The role of the arginine metabolome in pain: implications

for sickle cell disease. *Journal of Pain Research*, *9*, 167. https://doi.org/10.2147/JPR.S55571

Bar, K.-J., Brehm, S., Boettger, M. K., Boettger, S., Wagner, G., & Sauer, H. (2005). Pain perception in major depression depends on pain modality. *Pain*, *117*(1–2), 97–103. https://doi.org/10.1016/j.pain.2005.05.016

Barakat, L. P., Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Baron, R., Binder, A., & Wasner, G. (2010). Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology*, *9*(8), 807–819. https://doi.org/10.1016/S1474-4422(10)70143-5

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anaesthesia*, *111*(1), 52–58. https://doi.org/10.1093/bja/aet127

Bediako, S. M., Lanzkron, S., Diener-West, M., Onojobi, G., Beach, M. C., & Haywood, C. (2016). The Measure of Sickle Cell Stigma: Initial findings from the Improving Patient Outcomes through Respect and Trust study. *Journal of Health Psychology*, *21*(5), 808–820. https://doi.org/10.1177/1359105314539530

Bennett, M. I., Smith, B. H., Torrance, N., & Potter, J. (2005). The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinical and postal research. *The Journal of Pain*, *6*(3), 149–158. https://doi.org/10.1016/j.jpain.2004.11.007

Blair, M, Robinson, R, Katon, W, Kroenke, K. (2003). Depression and Pain Comorbidity. *Arch Intern Med*, *163*(20), 2433–2445. https://doi.org/10.1001/archinte.163.20.2433.

Bower, J. E. (2014). Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nature Reviews. Clinical Oncology*, *11*(10), 597–609. https://doi.org/10.1038/nrclinonc.2014.127

Brandow, A M, Farley, R. A., & Panepinto, J. A. (2014). Neuropathic pain in patients with sickle cell disease. *Pediatric Blood and Cancer*, *61*(3), 512–517. https://doi.org/10.1002/pbc.24838

Brandow, A M, Farley, R. A., & Panepinto, J. A. (2015). Early insights into the neurobiology of pain in sickle cell disease: A systematic review of the literature. *Pediatric Blood & Cancer*, *62*(9), 1501–1511. https://doi.org/10.1002/pbc.25574 [doi]

Brandow, Amanda M., Farley, R. A., & Panepinto, J. A. (2014). Neuropathic pain in patients with sickle cell disease. *Pediatric Blood & Cancer*. https://doi.org/10.1002/pbc.24838

Brandow, Amanda M., & Panepinto, J. A. (2016). Clinical Interpretation of quantitative sensory testing as a measure of pain sensitivity in patients with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *38*(4), 288–293. https://doi.org/10.1097/MPH.0000000000000532

Brandow, Amanda M., Stucky, C. L., Hillery, C. A., Hoffmann, R. G., & Panepinto, J. A. (2013). Patients with sickle cell disease have increased sensitivity to cold and heat. *American Journal of Hematology*. https://doi.org/10.1002/ajh.23341

Bridges, D., Thompson, S. W. N., & Rice, A. S. C. (2001). Mechanisms of neuropathic pain. *Br J Anaesth*, *87*(1), 12–26.

Brousseau, D C, Owens, P. L., Mosso, A. L., Panepinto, J. A., & Steiner, C. A. (2010). Acute care utilization and rehospitalizations for sickle cell disease. *Jama*, *303*(13), 1288–1294. https://doi.org/10.1001/jama.2010.378 [doi]

Brousseau, David C, Scott, J. P., Badaki-Makun, O., Darbari, D. S., Chumpitazi, C. E., Airewele, G. E., … Panepinto, J. A. (2015). A multicenter randomized controlled trial of intravenous magnesium for sickle cell pain crisis in children. *Blood*, *126*(14), 1651–1657. https://doi.org/10.1182/blood-2015-05-647107

Burgess, S. E., Gardell, L. R., Ossipov, M. H., Malan, T. P., Vanderah, T. W., Lai, J., & Porreca, F. (2002). Time-dependent descending facilitation from the rostral ventromedial medulla maintains, but does not initiate, neuropathic pain. *The Journal of Neuroscience*, *22*(12), 5129–5136. https://doi.org/22/12/5129 [pii]

Büssing, A., Ostermann, T., Lüdtke, R., & Michalsen, A. (2012). Effects of yoga interventions on pain and pain-associated disability: A meta-analysis. *Journal of Pain*, *13*(1), 1–9. https://doi.org/10.1016/j.jpain.2011.10.001

Campbell, C. M. ., Carroll, C. P. ., Kiley, K. ., Han, D. ., Haywood, C. ., Lanzkron, S. ., … Haythornthwaite, J. A. . (2016). Quantitative sensory testing and pain-evoked cytokine reactivity: Comparison of patients with sickle cell disease to healthy matched controls. *Pain*, *157*(4), 949–956. https://doi.org/10.1097/j.pain.0000000000000473

Campbell, C. M., Bounds, S. C., Simango, M. B., Witmer, K. R., Campbell, J. N., Edwards, R. R., … Smith, M. T. (2011). Self-reported sleep duration associated with distraction analgesia, hyperemia, and secondary hyperalgesia in the heat-capsaicin nociceptive model. *European Journal of Pain*, *15*(6), 561–567. https://doi.org/10.1016/j.ejpain.2010.11.014

Campbell, C. M., Moscou-Jackson, G., Carroll, C. P., Kiley, K., Haywood, C., Lanzkron, S., … Haythornthwaite, J. A. (2016). An Evaluation of Central Sensitization in Patients With Sickle Cell Disease. *The Journal of Pain*, *17*(5), 617–627. https://doi.org/10.1016/j.jpain.2016.01.475

Carr, D. B., & Goudas, L. C. (2013). Acute Pain. *British Journal of Pain*, *7*(2_suppl), 5–76. https://doi.org/10.1177/2049463713481587

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77.

https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, P. C., Haywood, C., Hoot, M. R., & Lanzkron, S. (2013). A preliminary study of psychiatric, familial, and medical characteristics of high-utilizing sickle cell disease patients. *Clinical Journal of Pain*, *29*(4), 317–323. https://doi.org/10.1097/AJP.0b013e3182579b87

Carter, B., Lambrenos, K., & Thursfield, J. (2002). A pain workshop: an approach to eliciting the views of young people with chronic pain. *Journal of Clinical Nursing*, *11*(6), 753–762.

Charache, S., Terrin, M. L., Moore, R. D., Dover, G. J., Barton, F. B., Eckert, S. V., … Bonds, D. R. (1995). Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. *New England Journal of Medicine*, *332*(20), 1317–1322. https://doi.org/10.1056/NEJM199505183322001

Chestnut, D. E. (1994). Perceptions of ethnic and cultural factors in the delivery of services in the treatment of sickle cell disease. *Journal of Health & Social Policy*, *5*(3–4), 215–242. https://doi.org/10.1300/J045v05n03_13

Ciechanowski, P., Sullivan, M., Jensen, M., Romano, J., & Summers, H. (2003). The relationship of attachment style to depression, catastrophizing and health care utilization in patients with chronic pain. *Pain*, *104*(3), 627–637.

Citero, V. de A., Levenson, J. L., McClish, D. K., Bovbjerg, V. E., Cole, P. L., Dahman, B. A., … Smith, W. R. (2007). The role of catastrophizing in sickle cell disease - The PiSCES project. *Pain*, *133*(1–3), 39–46. https://doi.org/10.1016/j.pain.2007.02.008

Clauw, D. J., & Chrousos, G. P. (1997). Chronic Pain and Fatigue Syndromes: Overlapping Clinical and Neuroendocrine Features and Potential Pathogenic Mechanisms. *Neuroimmunomodulation*, *4*, 134–153.

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: mechanisms and their clinical implications. *Bmj*, *348*(feb05 6), f7656–f7656. https://doi.org/10.1136/bmj.f7656

Costigan, M., Scholz, J., & Woolf, C. J. (2009). Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual Review of Neuroscience*, *32*, 1–32. https://doi.org/10.1146/annurev.neuro.051508.135531

Daniel, L. C., Grant, M., Kothare, S. V, Dampier, C., & Barakat, L. P. (2010). Sleep Patterns in Pediatric Sickle Cell Disease. *Pediatr Blood Cancer*, (October 2009), 501–507. https://doi.org/10.1002/pbc

Darbari, D. S., Hampson, J. P., Ichesco, E., Kadom, N., Vezina, G., Evangelou, I., … Harris, R. E. (2015). Frequency of Hospitalizations for Pain and Association with Altered Brain Network Connectivity in Sickle Cell Disease. *Journal of Pain*, *16*(11), 1077–1086. https://doi.org/10.1016/j.jpain.2015.07.005

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2017). The SPADE Symptom Cluster in Primary Care Patients with Chronic Pain. *Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286.The

De Ruddere, L., & Craig, K. D. (2016). Understanding stigma and chronic pain: a-state-of-the-art

review. *Pain*, *157*(8), 1607–1610. https://doi.org/10.1097/j.pain.0000000000000512

Diatchenko, L., Nackley, A. G., Slade, G. D., Fillingim, R. B., & Maixner, W. (2006). Idiopathic pain disorders - Pathways of vulnerability. *Pain*. https://doi.org/10.1016/j.pain.2006.04.015

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., … Maixner, W. (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics*, *14*(1), 135–143. https://doi.org/10.1093/hmg/ddi013

Dorsey, C., Phillips, K. D., & Williams, C. (2001). Adult sickle cell patients' perceptions of nurses' caring behaviors. *The ABNF Journal*, *12*(5), 95–100.

Dubin, A. E., & Patapoutian, A. (2010). Nociceptors: The sensors of the pain pathway. *Journal of Clinical Investigation*. https://doi.org/10.1172/JCI42843

Edwards, R. R., Almeida, D. M., Klick, B., Haythornthwaite, J. A., & Smith, M. T. (2008). Duration of sleep contributes to next-day pain report in the general population. *Pain*, *137*(1), 202–207. https://doi.org/10.1016/j.pain.2008.01.025

Emin Erdal, M., Herken, H., Yilmaz, M., & Bayazit, Y. A. (2001). Significance of the catechol-O-methyltransferase gene polymorphism in migraine. *Brain Research. Molecular Brain Research*, *94*(1–2), 193–196.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004

Ezenwa, M O, Molokie, R. E., Wang, Z. J., Yao, Y., Suarez, M. L., Pullum, C., … Wilkie, D. J. (2015). Safety and Utility of Quantitative Sensory Testing among Adults with Sickle Cell Disease: Indicators of Neuropathic Pain? *Pain Practice*, *16*(3), 282–293. https://doi.org/10.1111/papr.12279

Ezenwa, Miriam O., Yao, Y., Engeland, C. G., Molokie, R. E., Wang, Z. J., Suarez, M. L., & Wilkie, D. J. (2016). A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *Journal of Advanced Nursing*, *72*(6), 1452–1463. https://doi.org/10.1111/jan.12895

Fayaz, A., Croft, P., Langford, R. M., Donaldson, L. J., & Jones, G. T. (2016). Prevalence of chronic pain in the UK : a systematic review and meta-analysis of population studies. https://doi.org/10.1136/bmjopen-2015-010364

Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley, J. L. (2009). Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *Journal of Pain*, *10*(5), 447–485. https://doi.org/10.1016/j.jpain.2008.12.001

Finan, P H, Goodin, B. R., & Smith, M. T. (2014). The association of sleep and pain: An update and a path forward. *The Journal of Pain*, *14*(12), 1539–1552. https://doi.org/10.1016/j.jpain.2013.08.007.The

Finan, Patrick H, Carroll, C. P., Moscou-Jackson, G., Martel, M. O., Campbell, C. M., Pressman,

A., … Haythornthwaite, J. A. (2018). Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis. *The Journal of Pain*, *19*(1), 46–56. https://doi.org/10.1016/j.jpain.2017.08.010

Flor, H., & Turk, D. (2011). *Chronic pain: an integrated biobehavioral approach*. Seattle: IASP Press.

Ford, J. D., Grasso, D. J., Jones, S., Works, T., & Andemariam, B. (2017). Interpersonal Violence Exposure and Chronic Pain in Adult Sickle Cell Patients. *Journal of Interpersonal Violence*, 886260517691521. https://doi.org/10.1177/0886260517691521

Forgeron, P. A., King, S., Stinson, J. N., McGrath, P. J., MacDonald, A. J., & Chambers, C. T. (2010). Social functioning and peer relationships in children and adolescents with chronic pain: A systematic review. *Pain Research and Management*, *15*(1), 27–41. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-77950464526&partnerID=40&md5=1b217295f888cc94f5cc4d05615801ae

Gagliese, L. (2009). Pain and aging: the emergence of a new subfield of pain research. *The Journal of Pain*, *10*(4), 343–353. https://doi.org/10.1016/j.jpain.2008.10.013

Garip, Y., Eser, F., Aktekin, L. A., & Bodur, H. (2011). Fatigue in rheumatoid arthritis: association with severity of pain, disease activity and functional status. *Acta Reumatologica Portuguesa*, *36*(4), 364–369.

Garland, E. (2012). Pain Processing the Human Nervous System: A Selective Review of Nocicetive and Biobehavioral Pathway. *Primary Care*, *39*(3), 561–571. https://doi.org/10.1016/j.pop.2012.06.013.Pain

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581–624. https://doi.org/2007-09203-002 [pii]

Geisser, M. E., Robinson, M. E., Keefe, F. J., & Weiner, M. L. (1994). Catastrophizing, depression and the sensory, affective and evaluative aspects of chronic pain. *Pain*, *59*(1), 79–83.

Gladwin, M. T., Kato, G. J., Weiner, D., Onyekwere, O. C., Dampier, C., Hsu, L., … Casella, J. F. (2011). Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA*, *305*(9), 893–902. https://doi.org/10.1001/jama.2011.235

Graves, J. K., & Jacob, E. (2014). Pain, coping, and sleep in children and adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing*, *27*(3), 109–120. https://doi.org/10.1111/jcap.12077 [doi]

Green, C. R., Anderson, K. O., Baker, T. A., Campbell, L. C., Decker, S., Fillingim, R. B., … Vallerand, A. H. (2003). The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Medicine (Malden, Mass.)*, *4*(3), 277–294.

Green, C. R., & Hart-Johnson, T. (2010). The impact of chronic pain on the health of black and white men. *Journal of the National Medical Association*, *102*(4), 321–331.

Gross, C., & Hen, R. (2004). The developmental origins of anxiety. *Philosophical Transactions*

of the Royal Society B: Biological Sciences, *5*(1449), 1359–1366. https://doi.org/10.1098/rstb.2004.1518

Gur, A., Karakoc, M., Erdogan, S., Nas, K., Cevik, R., & Sarac, A. J. (2002). Regional cerebral blood flow and cytokines in young females with fibromyalgia. *Clinical and Experimental Rheumatology*, *20*(6), 753–760. https://doi.org/10.1108/IJWHM-07-2014-0026

Gursoy, S., Erdal, E., Herken, H., Madenci, E., Alasehirli, B., & Erdal, N. (2003). Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatology International*, *23*(3), 104–107. https://doi.org/10.1007/s00296-002-0260-5

Hanks, G. W., & LLOYD, J. W. (1986). Depression and anxiety in pain clinics. *Anaesthesia*, *41*(3), 326–326. https://doi.org/10.1111/j.1365-2044.1986.tb12803.x

Harris, R. E., Clauw, D. J., Scott, D. J., McLean, S. A., Gracely, R. H., & Zubieta, J.-K. (2007). Decreased Central -Opioid Receptor Availability in Fibromyalgia. *Journal of Neuroscience*, *27*(37), 10000–10006. https://doi.org/10.1523/JNEUROSCI.2849-07.2007

Harte, S. E., Harris, R. E., & Clauw, D. J. (2018). The neurobiology of central sensitization. *Journal of Applied Biobehavioral Research*, *23*(2). https://doi.org/10.1111/jabr.12137

Häuser, W., Jung, E., Erbslöh-Möller, B., Gesmann, M., Kühn-Becker, H., Petermann, F., … Wolfe, F. (2012). Validation of the fibromyalgia survey questionnaire within a cross-sectional survey. *PLoS ONE*, *7*(5), 3–8. https://doi.org/10.1371/journal.pone.0037504

Hauser, W., Kosseva, M., Uceyler, N., Klose, P., & Sommer, C. (2011). Emotional, physical, and sexual abuse in fibromyalgia syndrome: a systematic review with meta-analysis. *Arthritis Care & Research*, *63*(6), 808–820. https://doi.org/10.1002/acr.20328 [doi]

Heeney, M. M., Hoppe, C. C., Abboud, M. R., Inusa, B., Kanter, J., Ogutu, B., … Rees, D. C. (2016). A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events. *The New England Journal of Medicine*, *374*(7), 625–635. https://doi.org/10.1056/NEJMoa1512021

Heffner, K. L., France, C. R., Trost, Z., Mei Ng, H., & Pigeon, W. R. (2011). Chronic low back pain, sleep disturbance, and interleukin-6. *Clinical Journal of Pain*, *27*(1), 35–41. https://doi.org/10.1097/AJP.0b013e3181eef761

Helme, R. D., & Gibson, S. J. (2001). The epidemiology of pain in elderly people. *Clinics in Geriatric Medicine*, *17*(3), 417–431, v.

Higgins, N. C., Bailey, S. J., LaChapelle, D. L., Harman, K., & Hadjistavropoulos, T. (2015). Coping Styles, Pain Expressiveness, and Implicit Theories of Chronic Pain. *The Journal of Psychology*, *149*(7), 737–750. https://doi.org/10.1080/00223980.2014.977759

Holden, J. E., Jeong, Y., & Forrest, J. M. (2005). The endogenous opioid system and clinical pain management. *AACN Clinical Issues*, *16*(3), 291–301. https://doi.org/10.1097/00044067-200507000-00003

Holtzman, S., Newth, S., & Delongis, A. (2004). The role of social support in coping with daily pain among patients with rheumatoid arthritis. *Journal of Health Psychology*, *9*(5), 677–695. https://doi.org/10.1177/1359105304045381

Jacob, E, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*, *37*(3), 185–189. https://doi.org/10.1097/MPH.0000000000000214 [doi]

Jacob, Eufemia, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). *Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease*. *J Pediatr Hematol Oncol* (Vol. 37). Retrieved from www.jpho-online.com

Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary Care Companion for CNS Disorders*, *13*(2), 10.4088/PCC.10m01063. https://doi.org/10.4088/PCC.10m01063 [doi]

Jones, A. K. P. (1999). The contribution of functional imaging techniques to our understanding of rheumatic pain. *Rheumatic Disease Clinics of North America*, *25*(1).

Kalisch, R., Wiech, K., Critchley, H. D., Seymour, B., O'Doherty, J. P., Oakley, D. A., … Dolan, R. J. (2005). Anxiety reduction through detachment: subjective, physiological, and neural effects. *Journal of Cognitive Neuroscience*, *17*(6), 874–883. https://doi.org/10.1162/0898929054021184

Kanzawa-Lee, G. A., Knoerl, R., Williams, D. A., Clauw, D. J., Bridges, C. M., Harte, S. E., … Lavoie Smith, E. M. (2018). Childhood Trauma Predicts Cancer Treatment-Related Pain in Breast Cancer Survivors. *Cancer Nursing*. https://doi.org/10.1097/NCC.0000000000000687

Keefe, F. J., Lefebvre, J. C., Egert, J. R., Affleck, G., Sullivan, M. J., & Caldwell, D. S. (2000). The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain*, *87*(3), 325–334.

Kool, M. B., van Middendorp, H., Boeije, H. R., & Geenen, R. (2009). Understanding the lack of understanding: invalidation from the perspective of the patient with fibromyalgia. *Arthritis and Rheumatism*, *61*(12), 1650–1656. https://doi.org/10.1002/art.24922

Krueger, A. B., & Stone, A. A. (2008). Assessment of pain: a community-based diary survey in the USA. *Lancet*, *371*(9623), 1519–1525. https://doi.org/10.1016/S0140-6736(08)60656-X

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V, Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *The Journal of Neuroscience*, *34*(11), 3969–3975. https://doi.org/10.1523/JNEUROSCI.5055-13.2014

Labbe, E., Herbert, D., & Haynes, J. (2005). Physicians' attitude and practices in sickle cell disease pain management. *Journal of Palliative Care*, *21*(4), 246–251.

Laird, B. J., McMillan, D. C., Fayers, P., Fearon, K., Kaasa, S., Fallon, M. T., & Klepstad, P. (2013). The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. *The Oncologist*, *18*(9), 1050–1055. https://doi.org/10.1634/theoncologist.2013-0120

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *Journal of Pain*, *10*(9), 895–926.

https://doi.org/10.1016/j.jpain.2009.06.012

Lemanek, K. L., Ranalli, M., & Lukens, C. (2009). A randomized controlled trial of massage therapy in children with sickle cell disease. *Journal of Pediatric Psychology*, *34*(10), 1091–1096. https://doi.org/10.1093/jpepsy/jsp015

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*, *19*(3), 14–27.

Logan, D. E., Catanese, S. P., Coakley, R. M., & Scharff, L. (2007). Chronic pain in the classroom: teachers' attributions about the causes of chronic pain. *The Journal of School Health*, *77*(5), 248–256. https://doi.org/10.1111/j.1746-1561.2007.00200.x

Lopez-Martinez, A. E., Esteve-Zarazaga, R., & Ramirez-Maestre, C. (2008). Perceived social support and coping responses are independent variables explaining pain adjustment among chronic pain patients. *The Journal of Pain*, *9*(4), 373–379. https://doi.org/10.1016/j.jpain.2007.12.002 [doi]

Louati, K., & Berenbaum, F. (2016). Fatigue in chronic inflammation - a link to pain pathways. *Arthritis Research & Therapy*, (2015), 1–10. https://doi.org/10.1186/s13075-015-0784-1

Maletic, V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Frontiers in Bioscience*, *14*, 5291–5338.

Mansour, A. R., Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2014). Chronic pain: The role of learning and brain plasticity. *Restor Neurol Neurosc*, *32*(1), 129–139. https://doi.org/10.3233/RNN-139003.Chronic

Marchand, S. (2008). The Physiology of Pain Mechanisms: From the Periphery to the Brain. *Rheumatic Disease Clinics of North America*, *34*(2), 285–309. https://doi.org/10.1016/j.rdc.2008.04.003

Martin, S. R., Cohen, L. L., Mougianis, I., Griffin, A., Sil, S., & Dampier, C. (2018). Stigma and Pain in Adolescents Hospitalized for Sickle Cell Vasoocclusive Pain Episodes. *The Clinical Journal of Pain*, *34*(5), 438–444. https://doi.org/10.1097/AJP.0000000000000553 [doi]

May, A. (2008). Chronic pain may change the structure of the brain. *Pain*, *137*(1), 7–15. https://doi.org/10.1016/j.pain.2008.02.034

McClish, D. K., Smith, W. R., Dahman, B. A., Levenson, J. L., Roberts, J. D., Penberthy, L. T., … Bovbjerg, V. E. (2009). Pain site frequency and location in sickle cell disease: The PiSCES project. *Pain*, *145*(1–2), 246–251. https://doi.org/10.1016/j.pain.2009.06.029

McCracken, L. M., Matthews, A. K., Tang, T. S., & Cuba, S. L. (2001). A comparison of blacks and whites seeking treatment for chronic pain. *The Clinical Journal of Pain*, *17*(3), 249–255.

McEntire, D. M., Kirkpatrick, D. R., Dueck, N. P., Kerfeld, M. J., Smith, T. A., Nelson, T. J., … Agrawal, D. K. (2016). Pain transduction: a pharmacologic perspective. *Expert Review of Clinical Pharmacology*, *9*(8), 1069–1080. https://doi.org/10.1080/17512433.2016.1183481

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated

with chronic pain: An examination in a nationally representative sample. *Pain*, *106*(1–2), 127–133. https://doi.org/10.1016/S0304-3959(03)00301-4

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain*, *111*(1–2), 77–83. https://doi.org/10.1016/j.pain.2004.06.002

Medicine, I. of. (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13172

Merskey, H., & Bogduk, N. (1994). *Classification of chronic pain* (2nd ed.). Seattle: IASP Press.

Monsivais, D. B. (2013). Decreasing the stigma burden of chronic pain. *Journal of the American Association of Nurse Practitioners*, *25*(10), 551–556. https://doi.org/doi:10.1111/1745-7599.12010

Montoya, P., Larbig, W., Braun, C., Preissl, H., & Birbaumer, N. (2004). Influence of social support and emotional context on pain processing and magnetic brain responses in fibromyalgia. *Arthritis and Rheumatism*, *50*(12), 4035–4044. https://doi.org/10.1002/art.20660

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Morris, C. R., Kuypers, F. A., Lavrisha, L., Ansari, M., Sweeters, N., Stewart, M., … Vichinsky, E. P. (2013). A randomized, placebo-controlled trial of arginine therapy for the treatment of children with sickle cell disease hospitalized with vaso-occlusive pain episodes. *Haematologica*, *98*(9), 1375–1382. https://doi.org/10.3324/haematol.2013.086637

Moscou-Jackson, G., Finan, P. H., Campbell, C. M., Smyth, J. M., & Haythornthwaite, J. A. (2015). The effect of sleep continuity on pain in adults with sickle cell disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010

Nahin, R. L. (2015). Estimates of Pain Prevalence and Severity in Adults: United States, 2012. *Journal of Pain*, *16*(8), 769–780. https://doi.org/10.1016/j.jpain.2015.05.002

Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis and Rheumatism*, *62*(8), 2545–2555. https://doi.org/10.1002/art.27497

National Heart, Lung, and B. I. (2014). *Evidence-Based Management of Sickle Cell Disease: Expert Panel, 2014*. https://doi.org/10.1542/peds.2014-2986

Neville, S. J., Clauw, A. D., Moser, S. E., Urquhart, A. G., Clauw, D. J., Brummett, C. M., & Harte, S. E. (2018). Association between the 2011 Fibromyalgia Survey Criteria and Multisite Pain Sensitivity in Knee Osteoarthritis. *Clinical Journal of Pain*, *34*(10), 909–917. https://doi.org/10.1097/AJP.0000000000000619

Nicassio, P. M., Moxham, E. G., Schuman, C. E., & Gevirtz, R. N. (2002). The contribution of

pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain*, *100*(3), 271–279.

Nicholson, B. (2006). Differential diagnosis: nociceptive and neuropathic pain. *The American Journal of Managed Care*, *12*(9 Suppl), S256-62.

Niihara, Y., Miller, S. T., Kanter, J., Lanzkron, S., Smith, W. R., Hsu, L. L., … Vichinsky, E. P. (2018). A Phase 3 Trial of <scp>l</scp> -Glutamine in Sickle Cell Disease. *New England Journal of Medicine*, *379*(3), 226–235. https://doi.org/10.1056/NEJMoa1715971

NINDS. (2015). *National pain strategy: a comprehensive population health-level strategy for pain*. Retrieved from https://iprcc.nih.gov/s; default/files/HHSNational_Pain_Strategy_508C.pdf

O'Leary, J. D., Crawford, M. W., Odame, I., Shorten, G. D., & McGrath, P. a. (2013). Thermal Pain and Sensory Processing in Children With Sickle Cell Disease. *The Clinical Journal of Pain*, *30*(3), 244–250. https://doi.org/10.1097/AJP.0b013e318292a38e

Ochsner, K. N., Ludlow, D. H., Knierim, K., Hanelin, J., Ramachandran, T., Glover, G. C., & Mackey, S. C. (2006). Neural correlates of individual differences in pain-related fear and anxiety. *Pain*, *120*(1–2), 69–77. https://doi.org/10.1016/j.pain.2005.10.014

Oliveira, V. C., Ferreira, P. H., Ferreira, M. L., Tiburcio, L., Pinto, R. Z., Oliveira, W., & Dias, R. (2009). People with low back pain who have externalised beliefs need to see greater improvements in symptoms to consider exercises worthwhile: an observational study. *The Australian Journal of Physiotherapy*, *55*(4), 271–275.

Oram, S., Ostrovschi, N. V, Gorceag, V. I., Hotineanu, M. A., Gorceag, L., Trigub, C., & Abas, M. (2012). Physical health symptoms reported by trafficked women receiving post-trafficking support in Moldova: prevalence, severity and associated factors. *BMC Women's Health*, *12*, 20. https://doi.org/10.1186/1472-6874-12-20

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766

Pack-Mabien, A., Labbe, E., Herbert, D., & Haynes, J. J. (2001). Nurses' attitudes and practices in sickle cell pain management. *Applied Nursing Research : ANR*, *14*(4), 187–192. https://doi.org/10.1053/apnr.2001.26783

Palermo, T. M., & Kiska, R. (2005). Subjective sleep disturbances in adolescents with chronic pain: Relationship to daily functioning and quality of life. *Journal of Pain*, *6*(3), 201–207. https://doi.org/10.1016/j.jpain.2004.12.005

Park, J., & Chung, J. (2016). Inflammatory Cytokines and Sleep Disturbance in Patients with Temporomandibular Disorders. *Journal of Oral & Facial Pain and Headache*, *30*(1), 27–33. https://doi.org/10.11607/ofph.1367

Pavlin, D. J., Sullivan, M. J. L., Freund, P. R., & Roesen, K. (2005). Catastrophizing: a risk factor for postsurgical pain. *The Clinical Journal of Pain*, *21*(1), 83–90.

Perret, D., & Luo, Z. D. (2009). Targeting Voltage-Gated Calcium Channels for Neuropathic Pain Management. *Neurotherapeutics*, *6*(4), 679–692.

https://doi.org/10.1016/j.nurt.2009.07.006

Phillips, K, & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states--maybe it is all in their head. *Best Practice & Research.Clinical Rheumatology*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005 [doi]

Phillips, Kristine, & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states-maybe it is all in their head. *Best Pract Res Clin Rheumatol*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005

Pollard, L. C., Choy, E. H., Gonzalez, J., Khoshaba, B., & Scott, D. L. (2006). Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology*, *45*(7), 885–889. https://doi.org/10.1093/rheumatology/kel021

Quartana, P. J., & Edwards, R. R. (2009). Pain catastrophizing : a critical review, *9*(5), 745–758.

Rustoen, T., Wahl, A. K., Hanestad, B. R., Lerdal, A., Paul, S., & Miaskowski, C. (2005). Age and the experience of chronic pain: differences in health and quality of life among younger, middle-aged, and older adults. *The Clinical Journal of Pain*, *21*(6), 513–523.

Sarchielli, P., Mancini, M. L., Floridi, A., Coppola, F., Rossi, C., Nardi, K., … Calabresi, P. (2007). Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome. *The Journal of Pain*, *8*(9), 737–745. https://doi.org/10.1016/j.jpain.2007.05.002

Schaibl, H.-G., & Richter, F. (2004). Pathophysiology of pain. *Langenbecks Arch Surg*, *389*, 237–243. https://doi.org/10.1007/s00423-004-0468-9

Schaible, H.-G. (2014). Nociceptive neurons detect cytokines in arthritis. *Arthritis Research & Therapy*, *16*(5), 470.

Schatz, J., Schlenz, A. M., McClellan, C. B., Puffer, E. S., Hardy, S., Pfeiffer, M., & Roberts, C. W. (2015). Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *The Clinical Journal of Pain*, *31*(6), 536–547. https://doi.org/10.1097/AJP.0000000000000183 [doi]

Schlaeger, J. M., Molokie, R. E., Yao, Y., Suarez, M. L., Golembiewski, J., Wilkie, D. J., & Votta-Velis, G. (2017). Management of Sickle Cell Pain Using Pregabalin: A Pilot Study. *Pain Management Nursing*. https://doi.org/10.1016/j.pmn.2017.07.003

Schlenz, A. M., Schatz, J., & Roberts, C. W. (2016). Examining Biopsychosocial Factors in Relation to Multiple Pain Features in Pediatric Sickle Cell Disease. *Journal of Pediatric Psychology*, *41*(8), 930–940. https://doi.org/10.1093/jpepsy/jsw003 [doi]

Schofferman, J., Anderson, D., Hines, R., Smith, G., & Keane, G. (1993). Childhood psychological trauma and chronic refractory low-back pain. *The Clinical Journal of Pain*, *9*(4), 260–265.

Schrepf, A., Williams, D. A., Gallop, R., Naliboff, B. D., Basu, N., Kaplan, C., … Harte, S. E. (2018). Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study. *Pain*, *159*(10), 2002–2011. https://doi.org/10.1097/j.pain.0000000000001299

Severeijns, R., Vlaeyen, J. W., van den Hout, M. A., & Weber, W. E. (2001). Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *The Clinical Journal of Pain, 17*(2), 165–172.

Shapiro, B. S., Benjamin, L. J., Payne, R., & Heidrich, G. (1997). Sickle cell-related pain: perceptions of medical practitioners. *Journal of Pain and Symptom Management, 14*(3), 168–174. https://doi.org/10.1016/S0885-3924(97)00019-5

Shattuck, E. C., & Muehlenbein, M. P. (2016). Towards an integrative picture of human sickness behavior. *Brain, Behavior, and Immunity*, *57*, 255–262. https://doi.org/10.1016/j.bbi.2016.05.002

Sil, S, Cohen, L. L., & Dampier, C. (2016). Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *The Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289 [doi]

Sil, Soumitri, Cohen, L. L., & Dampier, C. (2016). Psychosocial and functional outcomes in youth with chronic sickle cell pain. *Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289

Skevington, S. M. (1990). A standardised scale to measure beliefs about controlling pain (B.P.C.Q.): A preliminary study. *Psychology & Health*, *4*(3), 221–232. https://doi.org/10.1080/08870449008400392

Smite, D., Rudzite, I., & Ancane, G. (2012). Sense of social support in chonic pain patients. *SHS Web of Conferences*, *2*, 00030. https://doi.org/10.1051/shsconf/20120200030

Smith, E. M., Bridges, C. M., Kanzawa, G., Knoerl, R., Kelly 4th, J. P., Berezovsky, A., & Woo, C. (2014). Cancer treatment-related neuropathic pain syndromes--epidemiology and treatment: an update. *Current Pain and Headache Reports*, *18*(11), 457–459. https://doi.org/10.1007/s11916-014-0459-7 [doi]

Smith, J. A., & Osborn, M. (2007). Pain as an assault on the self: An interpretative phenomenological analysis of the psychological impact of chronic benign low back pain. *Psychology & Health*, *22*(5), 517–534. https://doi.org/10.1080/14768320600941756

Smith, S. B., Maixner, D. W., Fillingim, R. B., Slade, G., Gracely, R. H., Ambrose, K., … Diatchenko, L. (2012). Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. *Arthritis and Rheumatism*, *64*(2), 584–593. https://doi.org/10.1002/art.33338

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., Mcclish, D. K., & Roberts, J. D. (2008). Daily Assessment of Pain in Adults with Sickle Cell Disease. *Annals of Internal Medicine*, *148*, 94–101. https://doi.org/10.7326/0003-4819-148-2-200801150-00004

Smith, W. R., & Scherer, M. (2010). Sickle-cell pain: advances in epidemiology and etiology. *Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program*. https://doi.org/10.1182/asheducation-2010.1.409

Smith, Y. R., Stohler, C. S., Nichols, T. E., Bueller, J. A., Koeppe, R. A., & Zubieta, J.-K. (2006). Pronociceptive and antinociceptive effects of estradiol through endogenous opioid

neurotransmission in women. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(21), 5777–5785. https://doi.org/10.1523/JNEUROSCI.5223-05.2006

Snelling, J. (1994). The effect of chronic pain on the family unit. *Journal of Advanced Nursing*, *19*(3), 543–551.

Spiegel, D. R., Chatterjee, A., McCroskey, A. L., Ahmadi, T., Simmelink, D., Oldfield 4th, E. C., … Raulli, O. (2015). A Review of Select Centralized Pain Syndromes: Relationship With Childhood Sexual Abuse, Opiate Prescribing, and Treatment Implications for the Primary Care Physician. *Health Services Research and Managerial Epidemiology*, *2*, 2333392814567920-Dec. https://doi.org/10.1177/2333392814567920 [doi]

Spinhoven, P., Ter Kuile, M., Kole-Snijders, A. M. J., Hutten Mansfeld, M., Den Ouden, D.-J., & Vlaeyen, J. W. S. (2004). Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *European Journal of Pain*, *8*(3), 211–219. https://doi.org/10.1016/j.ejpain.2003.08.003

Stone, K. C., Taylor, D. J., McCrae, C. S., Kalsekar, A., & Lichstein, K. L. (2008). Nonrestorative sleep. *Sleep Medicine Reviews*, *12*(4), 275–288. https://doi.org/10.1016/j.smrv.2007.12.002

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D. B., & Paulus, M. P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry*, *65*(11), 1275–1284. https://doi.org/10.1001/archpsyc.65.11.1275

Tanabe, P., Myers, R., Zosel, A., Brice, J., Ansari, A. H., Evans, J., … Paice, J. A. (2007). Emergency department management of acute pain episodes in sickle cell disease. *Academic Emergency Medicine*, *14*(5), 419–425. https://doi.org/10.1197/j.aem.2006.11.033

Taylor, A. M. W., Becker, S., Schweinhardt, P., & Cahill, C. (2016). Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction. *Pain*, *157*(6), 1194–1198. https://doi.org/10.1097/j.pain.0000000000000494

Tekur, P., Nagarathna, R., Chametcha, S., Hankey, A., & Nagendra, H. R. (2012). A comprehensive yoga programs improves pain, anxiety and depression in chronic low back pain patients more than exercise: an RCT. *Complementary Therapies in Medicine*, *20*(3), 107–118. https://doi.org/10.1016/j.ctim.2011.12.009

Thacker, M. A., Clark, A. K., Marchand, F., & McMahon, S. B. (2007). Pathophysiology of peripheral neuropathic pain: Immune cells and molecules. *Anesthesia and Analgesia*, *105*(3), 838–847. https://doi.org/10.1213/01.ane.0000275190.42912.37

Thomas, L. S., Stephenson, N., Swanson, M., Jesse, D. E., & Brown, S. (2013). A pilot study: the effect of healing touch on anxiety, stress, pain, pain medication usage, and physiological measures in hospitalized sickle cell disease adults experiencing a vaso-occlusive pain episode. *Journal of Holistic Nursing*, *31*(4), 234–247. https://doi.org/10.1177/0898010113491631

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., … Watanabe, M.

(2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The Journal of Pain : Official Journal of the American Pain Society, 9*(10), 883–891. https://doi.org/10.1016/j.jpain.2008.05.005

Ueda, H. (2008). Peripheral mechanisms of neuropathic pain - Involvement of lysophosphatidic acid receptor-mediated demyelination. *Molecular Pain, 4*, 5–7. https://doi.org/10.1186/1744-8069-4-11

Wade, J. B., Price, D. D., Hamer, R. M., Schwartz, S. M., & Hart, R. P. (1990). An emotional component analysis of chronic pain. *Pain, 40*(3), 303–310. https://doi.org/https://doi.org/10.1016/0304-3959(90)91127-5

Wakefield, E. O., Zempsky, W. T., Puhl, R. M., & Litt, M. D. (2018). Conceptualizing pain-related stigma in adolescent chronic pain: a literature review and preliminary focus group findings. *Pain Reports, 3*(7), 1–7. https://doi.org/10.1097/PR9.0000000000000679

Waldrop, R. D., & Mandry, C. (1995). Health professional perceptions of opioid dependence among patients with pain. *The American Journal of Emergency Medicine, 13*(5), 529–531. https://doi.org/10.1016/0735-6757(95)90163-9

Wallen, G. R., Minniti, C. P., Krumlauf, M., Eckes, E., Allen, D., Oguhebe, A., … Taylor, J. G. (2014). Sleep disturbance, depression and pain in adults with sickle cell disease. *BMC Psychiatry, 14*, 207. https://doi.org/10.1186/1471-244X-14-207

West, S. J., Bannister, K., Dickenson, A. H., & Bennett, D. L. (2015). Circuitry and plasticity of the dorsal horn - Toward a better understanding of neuropathic pain. *Neuroscience, 300*, 254–275. https://doi.org/10.1016/j.neuroscience.2015.05.020

Wilkie, D. J., Molokie, R., Boyd-Seal, D., Suarez, M. L., Kim, Y. O., Zong, S., … Wang, Z. J. (2010). Patient-reported outcomes: Descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. *Journal of the National Medical Association*. https://doi.org/10.1016/S0027-9684(15)30471-5

Williams, D. A. (2018). Phenotypic features of central sensitization. *Journal of Applied Biobehavioral Research, 23*(2), 1–15. https://doi.org/10.1111/jabr.12135

Williams, K. A., Petronis, J., Smith, D., Goodrich, D., Wu, J., Ravi, N., … Steinberg, L. (2005). Effect of Iyengar yoga therapy for chronic low back pain. *Pain, 115*(1–2), 107–117. https://doi.org/10.1016/j.pain.2005.02.016

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., … Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism, 46*(3), 319–329. https://doi.org/10.1016/j.semarthrit.2016.08.012

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. S., … Winfield, J. B. (2011). Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia. *Journal of Rheumatology, 38*(6), 1113–1122. https://doi.org/10.3899/jrheum.100594

Wolfe, F., Michaud, K., & Li, T. (2006). Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. *The Journal of Rheumatology*, *33*(10), 1942–1951.

Wolfe, F., Walitt, B. T., Rasker, J. J., Katz, R. S., & Häuser, W. (2015). The use of polysymptomatic distress categories in the evaluation of fibromyalgia (FM) and FM severity. *Journal of Rheumatology*, *42*(8), 1494–1501. https://doi.org/10.3899/jrheum.141519

Woolf, C. J. (2010). What is this thing called pain? *J Clin Inves*, *120*(11), 3742–3744. https://doi.org/10.1172/JCI45178.3742

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(SUPPL.3). https://doi.org/10.1016/j.pain.2010.09.030

Wun, T., Soulieres, D., Frelinger, A. L., Krishnamurti, L., Novelli, E. M., Kutlar, A., … Winters, K. J. (2013). A double-blind, randomized, multicenter phase 2 study of prasugrel versus placebo in adult patients with sickle cell disease. *Journal of Hematology and Oncology*, *6*(1), 1. https://doi.org/10.1186/1756-8722-6-17

Yezierski, R. P. (2013). The effects of age on pain sensitivity: Pre-clinical studies. *Pain Medicine*, *13*(Suppl 2), 1–15. https://doi.org/10.1111/j.1526-4637.2011.01311.x.THE

Zaza, C., & Baine, N. (2002). Cancer pain and psychosocial factors: a critical review of the literature. *Journal of Pain and Symptom Management*, *24*(5), 526–542.

Zempsky, W T, Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread Pain Among Youth With Sickle Cell Disease Hospitalized With Vasoocclusive Pain: A Different Clinical Phenotype? *The Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403 [doi]

Zempsky, William T., Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread pain among youth with sickle cell disease hospitalized with vasoocclusive pain. *Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403

Zempsky, William T. (2009). Treatment of sickle cell pain: fostering trust and justice. *JAMA*, *302*(22), 2479–2480. https://doi.org/10.1001/jama.2009.1811

Zempsky, William T, Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread Pain Among Youth With Sickle Cell Disease Hospitalized With Vasoocclusive Pain: A Different Clinical Phenotype? *The Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403

CHAPTER III

S.P.A.C.E. Symptom Cluster Among Adolescents and Adults with Sickle Cell Disease

Abstract

Introduction: Daily pain is a significant complication of sickle cell disease (SCD). Although pain impacts the lives of many patients with SCD, few pharmacologic and non-pharmacologic interventions are effective reduce pain among these patients. Research in other pain populations (e.g., fibromyalgia, low back pain) suggests that a centrally-mediated symptom cluster, S.P.A.C.E., may contribute to and exacerbate pain. No research studies have evaluated the severity and co-occurrence of S.P.A.C.E. symptoms among patients with SCD.

Purpose: The purpose of this research was 1) to describe the incidence and severity of six centrally-mediated S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, depression, cognitive function, and fatigue), and 2) to characterize the co-occurrence of S.P.A.C.E. symptoms, pain interference, opioid consumption morphine milliequivalents (MME), pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) measured via the body map within the GeoPain @ Home smartphone application.

Patients and Methods: Forty-eight adolescents and adults with SCD completed measures of S.P.A.C.E. symptoms, opioid consumption, and pain interference. After survey measure completion, participants reported current pain intensity and widespread pain using an interactive body map within the GeoPain @ Home smartphone application. Descriptive analyses were

conducted to evaluate the severity of S.P.A.C.E. symptoms, pain interference, opioid consumption, pain intensity, and P.A.I.N.S. Multiple Spearman correlations were calculated to characterize the co-occurrence of individual S.P.A.C.E. symptom severity scores, pain severity, opioid consumption, and pain interference.

Results: Forty-eight adolescents and young adults with SCD ages 14 to 35 ($\bar{X}$=22.8 years; *SD*=5.9) were included within the study. Sleep impairment ($\bar{X}$=56.63; *SD*=9.05) and fatigue ($\bar{X}$=52.99; *SD*=11.24) were the only S.P.A.C.E. symptoms with mean severity scores higher than normative sample means. Mean pain interference ($\bar{X}$=55.56; *SD*=10.91) was also higher than the normative sample mean. Participants' pain intensity scores were 3.41, on average (*SD*=2.57). Mean opioid consumption MME was 23.67 (*SD*=42.58) with a wide range of 0 to 246 MME. Sleep impairment, anxiety, depression, and fatigue were all moderately and significantly correlated with one another (*r* range=0.42-0.75; $p<0.001$). Further, cognitive function was negatively and moderately correlated with sleep impairment, anxiety, and fatigue (*r* range=-0.39 – -0.54). Besides depression, all S.P.A.C.E. symptoms were moderately and significantly correlated with pain interference ($p<0.001$). Sleep impairment, anxiety, depression, cognitive function, and fatigue were not significantly associated with opioid consumption, pain intensity, and P.A.I.N.S.

Conclusion: These findings support the co-occurrence of several centrally-mediated S.P.A.C.E. symptoms among adolescents and young adults with SCD. Further, many S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, cognitive function, fatigue) were moderately and significantly associated with pain interference. Comprehensive evaluation and management of S.P.A.C.E. symptoms may facilitate improvements in social, cognitive, emotional, and physical function among patients with SCD.

Background

Pain impacts the lives of many patients with sickle cell disease (SCD) and is the most common reason for health service utilization (Platt et al., 1991; Vacca Jr & Blank, 2017). Despite the impact pain has on patients with SCD, few pharmacologic and non-pharmacologic treatments effectively reduce the incidence and severity of daily pain (National Heart, Lung, 2014). Pain among patients with SCD is complex—many patients experience acute, nociceptive pain episodes, or vaso-occlusive crises, in addition to daily, chronic pain (Finan et al., 2018; McClish et al., 2009; Smith et al., 2008).

Empirical evidence suggests that many symptoms co-occur with pain and increase the associated burden experienced by patients with SCD (K Phillips & Clauw, 2011; D. A. Williams, 2018). Research in chronic pain populations (e.g., fibromyalgia, low back pain, and endometriosis) suggests that individuals with a personal history of centrally-mediated symptoms are more likely to transition from acute to chronic/centralized pain (Hanish, Lin-Dyken, & Han, 2017; Keller, Yang, Treadwell, & Hassell, 2017; Merriwether et al., 2017). These centrally-mediated symptoms, conceptualized as the S.P.A.C.E. symptom cluster, include sleep impairment, widespread pain, affective perturbation (anxiety and depression), cognitive impairment, and low energy (fatigue) (Williams, 2018).

S.P.A.C.E. symptoms are hypothesized to interact with each other via several body systems such as the immune and central nervous systems. First, regarding the immune system, increased levels of cytokines including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α,) among others, have been associated with increased levels of pain and fatigue (Bower, 2014; Schaible, 2014). Further, one meta-analysis provides evidence that IL-1β and IL-6 have significant relationships with the S.P.A.C.E. symptom cluster (Shattuck & Muehlenbein,

2016). It is hypothesized that S.P.A.C.E. symptoms may co-occur with increased levels of cytokines (e.g., IL-1β, IL-6) and TNF-α as an adaptive physiological response to preserve energy and promote recovery (Shattuck & Muehlenbein, 2016; Williams, 2018).

Second, pain processing areas within the central nervous system may also explain the relationships among S.P.A.C.E. symptoms and pain (Bar et al., 2005; Ochsner et al., 2006). Evidence suggests that patients who have anxiety and depression have increased activation of several areas within the brain that perceive pain stimuli (e.g., anterior cingulate cortex, amygdala, and insula)(Bar et al., 2005; Etkin et al., 2011; Maletic & Raison, 2009; Ochsner et al., 2006; Strigo et al., 2008). It is hypothesized that increased activation of pain perception areas may give rise to and exacerbate pain and S.P.A.C.E. symptoms (Bar et al., 2005; Etkin et al., 2011; Maletic & Raison, 2009; Ochsner et al., 2006; Strigo et al., 2008).

Empirical evidence suggests that S.P.A.C.E. symptoms may be present among patients with SCD (Ameringer et al., 2014; Jerrell et al., 2011; Sharma et al., 2015; Zempsky et al., 2017). Many research studies have supported the association between affective perturbation (anxiety and depression) and pain (Carroll et al., 2016a; Donohoe & Smith, 2018; Hoff, Palermo, Schluchter, Zebracki, & Drotar, 2006; Jerrell et al., 2011; Karafin et al., 2018; Sil, Cohen, et al., 2016). Empirical evidence also supports the association between sleep disturbances and pain (Graves & Jacob, 2014; Moscou-Jackson et al., 2015; Wallen et al., 2014). To our knowledge, only one study has investigated the relationship between fatigue and pain (Ameringer et al., 2014). Further, no studies have evaluated the association between cognitive function and pain within this population.

Although it is known that many patients present with more than one centrally-mediated symptom, to date, research among patients with SCD have only focused on one or two of the

S.P.A.C.E. symptom domains. This major gap in the literature highlights a need for a comprehensive evaluation of all S.P.A.C.E. symptoms. A thorough evaluation of the severity and co-occurrence of these symptoms within the SCD population may lead to improved pain management strategies in the future. Thus, using a prospective, cross-sectional study design the study aims were to: 1) the severity of S.P.A.C.E. symptoms and 2) the co-occurrence of S.P.A.C.E. symptoms, pain interference, opioid consumption MME, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.).

Methods

Sample and Setting

Adolescents and adults with SCD (*N*=48) were recruited between 8/2019-12/2020 from the Pediatric and Adult Comprehensive Sickle Cell Clinics at Mott Children's Hospital and Michigan Medicine. Patients were included in the study if they were between the ages of 14 and 35 and could speak and read English. Patients were excluded from the study if they did not own a smartphone. The study was approved by the University of Michigan Institutional Review Board.

Recruitment and Data Collection

The principal investigator (PI) or a trained research assistant pre-screened potentially eligible patients via chart review, consultation with the patients' providers, and/or direct discussion with potential participants over the phone. Patients, and, in the case of adolescents, their parent/guardian were approached during their clinic appointment. The PI or a trained research assistant obtained signed informed consent/assent after thorough discussion of study procedures as well as benefits and risks of participation. Two participants were consented and

completed data collection outside of the clinic because they did not have any upcoming clinic appointments.

After obtaining informed consent, participants reported baseline demographics, the six S.P.A.C.E. symptoms, opioid consumption, and pain interference using electronic Qualtrics™ surveys via a tablet computer. The order in which participants completed the S.P.A.C.E., opioid consumption and pain interference surveys was randomized via the randomizer element within Qualtrics™. Following baseline survey completion, the PI or research assistant instructed participants on how to download the GeoPain @ Home mobile application on their personal cell phones. Participants reported baseline pain intensity and widespread pain using an interactive body map within the mobile application.

Measures

Demographic Survey. Patients self-reported their age, sex, race, ethnicity, and sickle cell genotype within the Demographics survey. Self-reported sickle cell genotype was confirmed by the PI or research assistant via electronic medical record (EMR) abstraction.

PROMIS® Short Form v1.0-Sleep-Related Impairment 8a. The 8-item PROMIS® Short Form Sleep-Related Impairment measures perceptions of alertness, sleepiness, and tiredness during usual waking hours using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores meaning greater levels of sleep-related impairment. Empirical evidence supports the instrument's internal consistency reliability (α=0.92), concurrent validity, and sensitivity in healthy adolescents, females with centralized pain, and adults with SCD (Bernstein et al., 1994; Spinhoven et al., 2014).

ACR 2011 Fibromyalgia Survey Criteria. The ACR 2011 Fibromyalgia Survey criteria contains the 19-item Widespread Pain Index (WPI) subscale which evaluates the presence or absence of

pain over the last 7 days in 19 different body regions. Scores from the WPI (range = 0-19) were used to operationalize widespread pain in this study. Empirical evidence supports the measure's internal consistency reliability (α=0.71), sensitivity, specificity, responsiveness, and validity (content and convergent) in patients with centralized pain (Wolfe et al., 2016).

PROMIS® Short Form v1.0 – Depression 8b. The 8-item PROMIS® Depression Short Form measures negative mood, anhedonia, negative views of the self, and negative social cognition based on the previous 7 days using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of depression. This measure has demonstrated internal consistency reliability (α= 0.93), convergent validity, and sensitivity in adults with centralized pain and SCD (Keller et al., 2017; Kroenke, Yu, Wu, Kean, & Monahan, 2014).

PROMIS® Short Form v1.0 Anxiety 8a. PROMIS® Anxiety Short Form measures fear, anxious misery, and hyper-arousal based on the previous 7 days using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of anxiety. This measure has demonstrated internal consistency reliability (α= 0.85), convergent and discriminant validity, and unidimensionality among adults with centralized pain (Irwin et al., 2010; Merriwether et al., 2017)

Multidimensional Inventory of Subjective Cognitive Impairment (MISCI). The 10-item MISCI quantifies perceived cognitive abilities and difficulties over the past seven days including mental clarity, memory, attention, executive functioning, and language on a 5-point Likert-type scale. Raw scores range from 10 to 50 with higher scores indicating better perceived cognitive functioning or lower cognitive impairment (Kratz, Schilling, Goesling, & Williams, 2015).

Empirical evidence supports the MISCI's internal consistency reliability (α=0.94), and construct and convergent validity among adults with centralized pain (Kratz et al., 2015).

PROMIS® Short Form v1.0-Fatigue 8a. The 8-item PROMIS® Fatigue Short Form measures the impact and experience of fatigue in the past week using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of fatigue. Empirical evidence supports the instrument's internal consistency reliability (α=0.83), test-retest reliability (ICC=0.85), concurrent and divergent validity, and sensitivity in adolescents and adults with SCD (Amtmann et al., 2010; Broderick, Schneider, Junghaenel, Schwartz, & Stone, 2013; Keller et al., 2017).

PROMIS® Short Form v1.0 – Pain Interference 4a. The 8-item PROMIS® Pain Interference Short Form assesses the self-reported consequences of pain on social, cognitive, emotional, physical, and recreational activities on the previous 7 days using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating more activity interference due to pain (Cella et al., 2010). Empirical evidence supports the measures' internal consistency reliability (α= 0.90 to 0.99), test-retest reliability (ICC 0.83 to 0.95), and sensitivity in adolescents and adults with centralized pain (Amtmann et al., 2010; Broderick et al., 2013).

Opioid Consumption. Participants reported their opioid consumption via a Qualtrics™ survey. Within the opioid consumption survey, participants reported which, if any, opioids they were taking, and the average number of pills taken per day within the previous seven days. The PI or trained research assistant collected information regarding prescribed opioid dosages via the EMR and calculated average daily milligram morphine equivalents (MME) for each participant using the Oregon Pain Guidance Opioid Conversion Calculator (2017).

GeoPain @ Home Mobile Application. Participants reported current pain intensity and widespread pain using the interactive body map within the GeoPain™ @ Home smartphone application (app) (MoxyTech Inc., MI). This commercial app is a derivative of a mobile app developed at the University of Michigan to optimize data collection among patients with migraines, dental pain, and cancer pain (DaSilva et al., 2014; DosSantos et al., 2012; MoxyTech Inc., MI). Empirical evidence supports the convergent validity and sensitivity of app in patients with centralized pain (DaSilva et al., 2014; Donnell et al., 2015; DosSantos et al., 2012; Nascimento et al., 2014). Figure 3 depicts the body map within the GeoPain @ Home app. Within the body map, participants report their pain intensity using a color scale from 0 to 10 (using a slider bar) and shade the area of the body that corresponds to the chosen intensity. The body map allows participants to change the pain intensity report for different areas of the body. The following three variables were calculated using the GeoPain @ Home body map:

Pain intensity. Pain intensity was calculated by averaging all self-reported pain intensity scores within the body map. Scores range from 0-10, with 0 meaning no pain.

Widespread pain. We evaluated widespread pain using the widespread pain index within the ACR 2011 Fibromyalgia Survey Criteria. To be more precise, we also evaluated widespread pain using the GeoPain @ Home body map. Within the body map, widespread pain is the percent of the body covered by painted pain cells. GeoPain widespread pain scores range from 0 to 100% with 100% indicating all body cells are painted.

P.A.I.N.S. Pain Area and Intensity Number Summation, or P.A.I.N.S., combines both pain intensity and widespread pain (DaSilva et al., 2014; MoxyTech Inc., MI). To derive P.A.I.N.S. percentage scores, pain intensity and widespread pain are multiplied together and divided by the total body area with maximum severe pain (pain intensity*widespread pain / 2026

[total body area] x 10 [maximum severe pain]). P.A.I.N.S. scores range from 0 to 100% with 100% indicating maximum severe pain (10/10) throughout the entire body area. Emerging empirical evidence supports the divergent validity of P.A.I.N.S. scores with μ-opioid activation measured during positron emission tomography (PET) sessions (DaSilva et al., 2014).

Statistical Analyses

Electronic survey and mobile application data were exported from Qualtrics™ and the GeoPain @ Home internet server and analyzed using Stata software (StataCorp, 2017). Descriptive statistics of the centrality and dispersion of all S.P.A.C.E. symptoms were calculated and plotted. Descriptive statistics (e.g. means, frequencies, 95% confidence intervals, and standard deviations) were calculated for all variables including demographic characteristics, six symptoms within the S.P.A.C.E. symptom cluster, opioid consumption MME, pain interference, pain intensity, and P.A.I.N.S. For all PROMIS® measures, the raw total scores were converted to T-scores (mean=50, standard deviation=10) using the PROMIS® Health Measures Scoring Service ("PROMIS® Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS®) (Version 1.1.v 9)"). Cognitive function raw scores were also converted to PROMIS® equivalent T-scores based on previously published conversion values (Kratz et al., 2015).

Opioid Consumption Survey responses were compared with corresponding electronic medical record (EMR) dosages and converted to average daily morphine milliequivalents (MME) using the Oregon Pain Guidance Opioid Conversion Calculator (2017). Some participants (*n*=6) reported taking opioids that were discontinued. In these instances, average daily opioid consumption MME was calculated using dosages from the discontinued prescription. Three participants reported taking codeine with no EMR prescription history within

three opioid consumption diaries. In these instances, average daily opioid consumption MME was calculated based on standard adult-specific dosages of codeine/acetaminophen (30/300mg)(Michigan Medicine Clinical Care Guidelines, 2016).

Spearman correlation coefficients were calculated to characterize the co-occurrence of individual S.P.A.C.E. symptom severity scores (i.e., sleep impairment, multifocal pain, anxiety, depression, cognitive function, and fatigue), average daily opioid consumption, pain interference, pain intensity, and P.A.I.N.S. The Bonferroni correction (Bonferroni, 1935) was used to account for multiple pairwise correlations.

Results

Demographics

Forty-eight adolescents and young adults completed S.P.A.C.E. symptom measures. Figure 4 identifies the number of patients that were screened, ineligible, and those who declined to participate in the study. The three main reasons patients declined to be in the study were 1) an inability to complete study measures due to time constraints, 2) patients did not feel comfortable downloading GeoPain @ Home app on personal smartphone, and 3) lack of interest.

Sample demographic information is presented in Table 2. Participants within the sample had a mean age of 22.8 years (range: 14-35 years). The majority of the sample was female (56.4%), African American (97.9%), and non-Hispanic (97.9%). The most common sickle cell genotypes were HbSS (72.9%) or HbSC (20.8%). Lastly, the majority of participants received some college education or technical training (33.3%), received a university degree (25%), or were in high school (22.9%).

Descriptive statistics of all S.P.A.C.E. variables are provided in Table 3. Participants reported pain in 4 out of 19 different body regions, on average. Mean cognitive function, anxiety,

and depression severity were approximately equal or lower than PROMIS® (or equivalent) normative sample means. Sleep impairment ($\bar{X}$=56.63), and fatigue ($\bar{X}$=52.99) were the only symptoms that were higher than PROMIS® normative sample means, with sleep impairment approximately 0.5 standard deviations above the normative sample mean.

Table 4 provides descriptive information regarding opioid consumption, pain interference, GeoPain widespread pain, pain intensity, and P.A.I.N.S. Average daily opioid consumption MME varied widely among participants with a range from 0 to 246 MME. Participants reported pain interference scores approximately 0.5 standard deviations higher than the PROMIS® normative sample mean. Although scores ranged throughout the sample, widespread pain, pain intensity, and P.A.I.N.S. mean scores were relatively low.

Pairwise correlations among all S.P.A.C.E. variables, average daily opioid consumption MME, pain interference, pain intensity, and P.A.I.N.S are presented in Table 5. Several S.P.A.C.E. variables were significantly correlated with one another (p<0.001) after correcting for multiple comparisons. Specifically, sleep impairment, anxiety, depression, and fatigue were all moderately correlated with one another (r range = 0.42-0.75). Further, cognitive function was negatively and moderately associated with sleep impairment, anxiety, and fatigue (r range = -0.39-0.54); however, correlations between cognitive function and anxiety were not statistically significant. Widespread pain was the only S.P.A.C.E. variable that was not significantly correlated with other S.P.A.C.E. variables; however, widespread pain was moderately correlated with fatigue.

Besides depression, all S.P.A.C.E. symptoms were moderately and significantly correlated with pain interference (p < 0.001). Widespread pain was the only S.P.A.C.E. variable that had a significant and moderate correlation with average daily opioid consumption (r = 0.47).

Besides, widespread pain, no S.P.A.C.E. variables were significantly correlated with opioid consumption, pain intensity, and P.A.I.N.S.

Discussion

This study described the severity and co-occurrence of physiologic and psychologic S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, depression, cognitive function, and fatigue) among adolescents and adults with SCD. Most S.P.A.C.E. symptom severity scores were comparable to PROMIS® (or equivalent) normative sample means. Sleep impairment and fatigue were the only two symptoms with higher mean severity than PROMIS® normative sample means. These findings are consistent with research that has evaluated incidence and severity of fatigue and sleep impairment among patients with SCD (Ameringer et al., 2014; Daniel et al., 2010; Mann-Jiles, Thompson, & Lester, 2015; Moody et al., 2017; Sharma et al., 2015).

There is conflicting evidence regarding the incidence and severity of anxiety and depression among patients with SCD (Bakshi et al., 2018; Jerrell et al., 2011; Laurence, George, Woods, & Baltimore, 2006; Ozer, Yengil, Acipayam, & Kokacya, 2014). Mean depression and anxiety scores of participants in the current study were lower (better) than normative sample means, on average. These low mean scores may be explained by low pain severity within our sample. Empirical evidence supports the association among anxiety, depression, and pain (Keller et al., 2017). The mean pain intensity ($\bar{X}$=3.41) within our study highlights that many participants had no or minimal pain. Thus, it is possible that depression and anxiety severity was low due to low pain intensity. Depression and anxiety scores may have been higher if our study targeted a sample with greater pain intensity.

Participants in our study reported better perceived cognitive functioning than normative sample mean scores, on average. To our knowledge, no research studies have evaluated perceived cognitive function among patients with SCD. Widespread pain varied among study participants; however, many participants (*n*=27) reported pain within three or more multiple different body sites. These findings add to the emerging evidence that widespread pain is present among a subset of patients with SCD (McClish et al., 2009; Zempsky et al., 2017).

Interestingly, widespread pain was the only S.P.A.C.E. symptom that was not significantly correlated with any other symptoms. The lack of statistically significant correlations among widespread pain and other centrally-mediated symptoms suggests that it may not be a valid contributor to the S.P.A.C.E. symptom cluster. Limited research has investigated the relationships among S.P.A.C.E. symptoms and widespread pain. To our knowledge, only one study supports a significant positive relationship between widespread pain and one symptom within S.P.A.C.E—depression (McClish et al., 2009). This study, however, dichotomized those with and without depression based on scores of a continuous patient-reported outcome measure, threatening the precision and statistical conclusion validity of the significant findings. To quantify depression in our sample, we utilized the PROMIS® Depression Short Form (SF) which has been psychometrically validated in SCD populations (Keller et al., 2017; Kroenke et al., 2014). Thus, the conflicting evidence between our study and one other (McClish et al., 2009) may be explained by differences in how depression was evaluated.

Besides widespread pain, our study highlighted that many S.P.A.C.E. symptoms were moderately and significantly correlated with one another. Sleep impairment and fatigue moderately correlated with three out of the four remaining S.P.A.C.E. symptoms—anxiety, depression, and cognitive function. Further many S.P.A.C.E. symptoms (i.e., sleep impairment,

widespread pain, anxiety, cognitive function, and fatigue) were moderately and significantly associated with pain interference. Further, our findings suggest that centrally-mediated symptoms have an association with pain interference, or the impact pain has on social, cognitive, emotional, and physical function (Amtmann et al., 2010). These findings are consistent with previous research that supports similar relationships among centrally-mediated symptoms in non-SCD populations (Davis et al., 2017; Robert Knoerl et al., 2018; Shattuck & Muehlenbein, 2016). Comprehensive evaluation and management of S.P.A.C.E. symptoms may facilitate improvements in social, cognitive, emotional, and physical function among patients with SCD. However, many S.P.A.C.E. symptoms may not be considered when evaluating patients during routine outpatient clinic visits. Symptom severity in our study was evaluated during outpatient clinic visits using PROMIS® short form patient-reported outcome (PRO) measures. Many patients were able to complete these measures while waiting to see their provider. Further, PROMIS® provides interpretable score ranges that correspond to within normal limits, mild, moderate, and severe. Evaluating S.P.A.C.E. symptoms in clinical settings—perhaps with PROMIS® short form measures—can facilitate individualized pain management approaches such as referrals to specialists (e.g., integrative health and palliative care providers) and ancillary psychiatric resources.

This study also evaluated the relationships among S.P.A.C.E. symptoms, average daily opioid consumption, and pain. Widespread pain was the only S.P.A.C.E. symptom significantly correlated with opioid consumption, pain intensity, and P.A.I.N.S. Since widespread pain and P.A.I.N.S. are both constructs operationalized based on the distribution of pain, strong and significant correlations were expected.

Low correlations among the remaining S.P.A.C.E. symptoms (sleep impairment, anxiety, depression, cognitive function, and fatigue), average daily opioid consumption, and pain conflict with empirical evidence among patients with SCD (Ameringer et al., 2014; Carroll et al., 2016b James L. Levenson et al., 2008; Moscou-Jackson, Gyasi, Finan, Campbell, & Smyth, Joshua M., Haythornthwaite, 2016). These conflicting findings may be explained by low symptom severity and our small sample size. First, anxiety and depression severity were low compared to PROMIS® normative sample means. Further, based on the mean pain intensity score ($\bar{X}$=3.41), many participants reported no or minimal pain. Low symptom severity may have limited our ability to report accurate correlations among S.P.A.C.E. symptoms, opioid consumption, and pain. Second, our small sample size may have increased the probability of a Type II error (false negative).

This study has several limitations. First, although this study included both adolescents and young adults from two separate outpatient clinics, the sample population was recruited from only one academic medical center. Thus, this sample is not fully representative of all adolescents and young adults with SCD. Second, many patients (*n*=6) self-reported taking opioids that were not documented in the EMR. Half of these patients (*n*=3) reported taking an opioid that had been discontinued. Empirical evidence suggests that many patients save opioids that have been previously prescribed and use them to manage subsequent pain episodes without provider guidance/authority (McCabe, West, & Boyd, 2013; Voepel-Lewis, Wagner, & Tait, 2015). Further, one self-reported opioid consumption diary was excluded based on suspected entry error. Overall, baseline self-reported opioid consumption reports may have been biased due to entry error and recall bias. Third, threats to statistical conclusion validity (i.e., low symptom severity, small sample size) may have limited the ability to accurately report correlations among

S.P.A.C.E. symptoms, opioid consumption, and pain. Lastly, although these findings support significant associations between several centrally-mediated symptoms and pain interference, the study's cross-sectional design limits the ability to make causal inferences among S.P.A.C.E. symptoms and pain.

In conclusion, this study is the first to evaluate the severity and co-occurrence of all symptoms within a symptom cluster, S.P.A.C.E. Our study found that multiple S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, cognitive function, and fatigue) and pain interference are moderately and significantly associated. Our study also found that widespread pain was the only S.P.A.C.E. symptom associated with opioid consumption. Due to the cross-sectional design of the current study, further research that evaluates the predictive relationships among S.P.A.C.E. symptoms, pain interference, and opioid consumption longitudinally is needed.

TABLE 2

Demographic Characteristics, N=48

Variable	*N (%)*
Age	
Mean (SD)	22.8 (5.9)
Range	14-35
Sex	
Female	27 (56.4)
Male	21 (43.8)
Race	
African American	47 (97.9)
More than one race	1 (2.1)
Ethnicity	
Not Hispanic or Latino	47 (97.9)
Unknown or do not wish to report	1 (2.1)
Education	
In middle school	1 (2.1)
In high school	11 (22.9)
Did not complete high school	3 (6.3)
Completed high school	4 (8.3)
Some college or technical training	16 (33.3)
University undergraduate degree	12 (25)
University post graduate degree	1 (2.1)
Sickle Cell Genotype	
HbSS	35 (72.9)
HbSC	10 (20.8)
HbSβ0	1 (2.1)
HbSβ+	2 (4.2)

TABLE 3

Descriptive Statistics of S.P.A.C.E. Symptoms, N=48

Variable	*Mean*	*SD*	*Minimum*	*Maximum*
PROMIS® Sleep Impairment SF	56.63	9.05	30	75
Widespread Pain Index	4.02	3.55	0	12
PROMIS® Depression SF	47.17	9.53	37.1	73.5
PROMIS® Anxiety SF	49.88	11.42	37.1	80
MISCI	50.33	4.63	44	61
PROMIS® Fatigue SF	52.99	11.24	33.1	77.7

Note. SD=standard deviation; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=short form; MISCI=Multidimensional Inventory of Subjective Cognitive Impairment

TABLE 4

Descriptive Statistics of Pain Variables, N=48

Variable	*Mean*	*SD*	*Minimum*	*Maximum*
Opioid Consumption MME+	22.1	42.58	0	246
PROMIS® Pain Interference SF	55.56	10.91	41.6	75.6
Pain Intensity*	3.41	2.57	0	9.71
Widespread Pain (GeoPain)*	2.79%	3.21	0%	13.82%
P.A.I.N.S.*	1.25%	1.73	0%	7.19%

Note. SD=standard deviation; MME=Morphine Milliequivalents; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=Short Form; P.A.I.N.S.=Pain Area and Intensity Number Summation; +Outlier excluded (*n*=47); *pain intensity, widespread pain, and P.A.I.N.S. data were only available for *n*=45

Table 5

Pairwise Correlations, N=48

Item Number	1	2	3	4	5	6	7	8	9	10	11
(1) Sleep Impairment	1.00										
(2) Widespread Pain	0.26	1.00									
(3) Anxiety	0.49*	0.21	1.00								
(4) Depression	0.46*	0.20	0.75*	1.00							
(5) Cognitive Function	-0.54*	-0.28	-0.39	-0.26	1.00						
(6) Fatigue	0.56*	0.37	0.53*	0.42*	-0.44*	1.00					
(7) Opioid Consumption+	0.25	0.51*	0.27	0.10	-0.17	0.31	1.00				
(8) Pain Interference	0.49*	0.65*	0.47*	0.28	-0.45*	0.59*	0.57*	1.00			
(9) Pain Intensity	0.33	0.50*	0.21	0.15	-0.35	0.40	0.28	0.42	1.00		
(10) Widespread Pain (GeoPain)	0.17	0.66*	0.22	0.06	-0.20	0.23	0.31	0.53*	0.51*	1.00	
(11) P.A.I.N.S.	0.28	0.67*	0.28	0.13	-0.35	0.35	0.35	0.58*	0.76*	0.92*	1.00

Note. P.A.I.N.S. data was only available for N=45; *Indicates significant correlation after Bonferroni correction p<0.0009; +Outlier excluded (n=47)

Figure 3

GeoPain @ Home Mobile Application Body Map

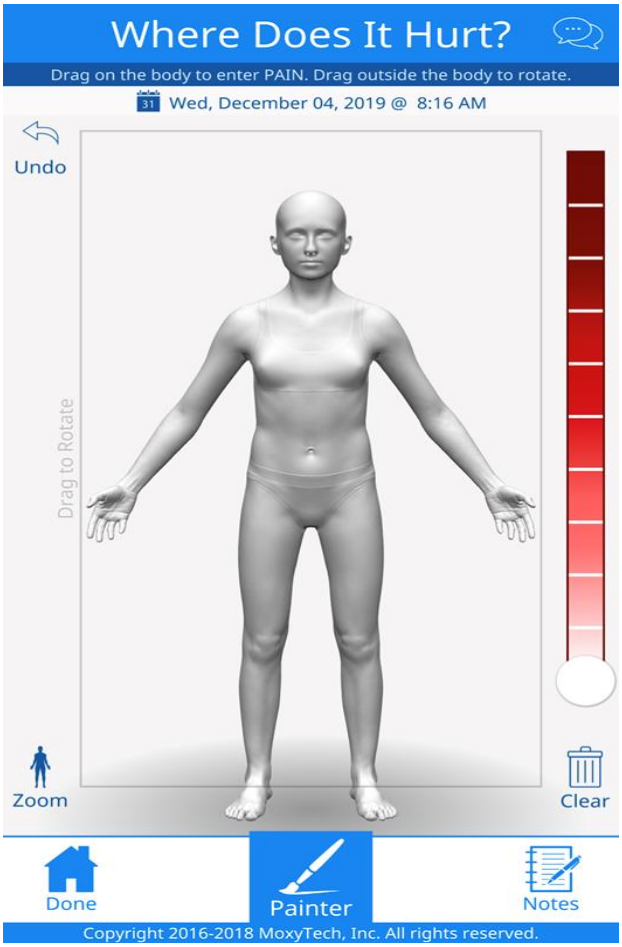
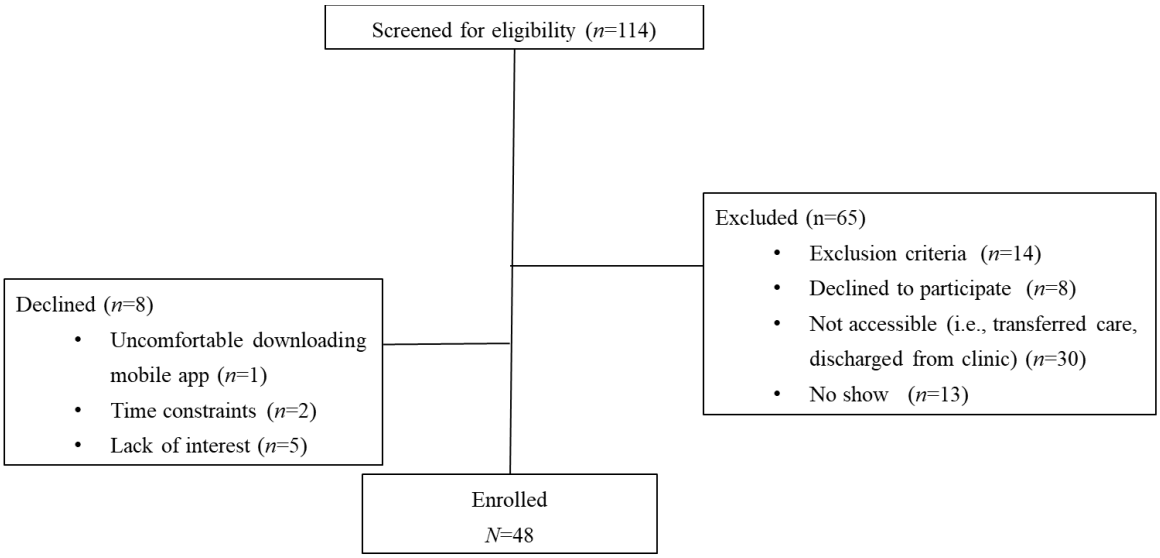


Figure 4

Consort Flow Diagram of Study Sample



References

Ameringer, S., Elswick Jr, R. K., & Smith, W. (2014). Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing*, *31*(1), 6–17. https://doi.org/10.1177/1043454213514632 [doi]

Amtmann, D., Cook, K. F., Jensen, M. P., Chen, W. H., Choi, S., Revicki, D., … Lai, J. S. (2010). Development of a PROMIS item bank to measure pain interference. *Pain*, *150*(1), 173–182. https://doi.org/10.1016/j.pain.2010.04.025 [doi]

Bakshi, N., Lukombo, I., Belfer, I., & Krishnamurti, L. (2018). Pain catastrophizing is associated with poorer health-related quality of life in pediatric patients with sickle cell disease. *Journal of Pain Research*, 947–953.

Bakshi, N., Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Bankar, M. A., Chaudhari, S. K., & Chaudhari, K. D. (2013). Impact of long term Yoga practice on sleep quality and quality of life in the elderly. *Journal of Ayurveda and Integrative Medicine*, *4*(1), 28–32. https://doi.org/10.4103/0975-9476.109548

Bar, K.-J., Brehm, S., Boettger, M. K., Boettger, S., Wagner, G., & Sauer, H. (2005). Pain perception in major depression depends on pain modality. *Pain*, *117*(1–2), 97–103. https://doi.org/10.1016/j.pain.2005.05.016

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132 [doi]

Bonferroni, C. E. (1935). *Il calcolo delle assicurazioni su gruppi di teste*. Rome.

Bower, J. E. (2014). Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nature Reviews. Clinical Oncology*, *11*(10), 597–609. https://doi.org/10.1038/nrclinonc.2014.127

Broderick, J. E., Schneider, S., Junghaenel, D. U., Schwartz, J. E., & Stone, A. A. (2013). Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. *Arthritis Care & Research*, *65*(10), 1625–1633. https://doi.org/10.1002/acr.22025

Brummett, C. M., Janda, A. M., Schueller, C. M., Tsodikov, A., Morris, M., Williams, D. A., & Clauw, D. J. (2013). Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology*, *119*(6), 1434–1443. https://doi.org/10.1097/ALN.0b013e3182a8eb1f [doi]

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical Psychology Review*,

26(1), 17–31. https://doi.org/10.1016/j.cpr.2005.07.003

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77. https://doi.org/10.1016/j.amepre.2016.02.012

Daniel, L. C., Grant, M., Kothare, S. V, Dampier, C., & Barakat, L. P. (2010). Sleep Patterns in Pediatric Sickle Cell Disease. *Pediatr Blood Cancer*, (October 2009), 501–507. https://doi.org/10.1002/pbc

DaSilva, A. F., Nascimento, T. D., DosSantos, M. F., Lucas, S., van HolsbeecK, H., DeBoer, M., … Zubieta, J.-K. (2014). Association of mu-Opioid Activation in the Prefrontal Cortex with Spontaneous Migraine Attacks - Brief Report I. *Annals of Clinical and Translational Neurology*, *1*(6), 439–444. https://doi.org/10.1002/acn3.65

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2017). The SPADE Symptom Cluster in Primary Care Patients with Chronic Pain. *Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286.The

Donohoe, C., & Smith, E. L. (2018). Psychological Predictors of Pain in Children and Adolescents With Sickle Cell Disease: A Scoping Review. *Journal of Pediatric Oncology Nursing : Official Journal of the Association of Pediatric Oncology Nurses*, 1043454218819457. https://doi.org/10.1177/1043454218819457

DosSantos, M. F., Martikainen, I. K., Nascimento, T. D., Love, T. M., Deboer, M. D., Maslowski, E. C., … DaSilva, A. F. (2012). Reduced basal ganglia mu-opioid receptor availability in trigeminal neuropathic pain: a pilot study. *Molecular Pain*, *8*, 74. https://doi.org/10.1186/1744-8069-8-74

Eller-smith, O. C., Nicol, A. L., Christianson, J. A., & Barr, G. A. (2018). Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions, *12*(February), 1–18. https://doi.org/10.3389/fncel.2018.00035

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004

Finan, P. H., Carroll, C. P., Moscou-Jackson, G., Martel, M. O., Campbell, C. M., Pressman, A., … Haythornthwaite, J. A. (2018). Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis. *The Journal of Pain*, *19*(1), 46–56. https://doi.org/10.1016/j.jpain.2017.08.010

Ghaffarilaleh, G., Ghaffarilaleh, V., Sanamno, Z., Kamalifard, M., & Alibaf, L. (2019). Effects of Yoga on Quality of Sleep of Women With Premenstrual Syndrome. *Alternative Therapies in Health and Medicine*, *25*(5), 40–47.

Graves, J. K., & Jacob, E. (2014). Pain, coping, and sleep in children and adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing*, *27*(3), 109–120. https://doi.org/10.1111/jcap.12077 [doi]

Hanish, A. E., Lin-Dyken, D. C., & Han, J. C. (2017). PROMIS Sleep Disturbance and Sleep-Related Impairment in Adolescents: Examining Psychometrics Using Self-Report and Actigraphy. *Nursing Research*, *66*(3), 246–251. https://doi.org/10.1097/NNR.0000000000000217 [doi]

Hassett, A. L., & Williams, D. A. (2011). Non-pharmacological treatment of chronic widespread musculoskeletal pain. *Best Practice & Research. Clinical Rheumatology*, *25*(2), 299–309. https://doi.org/10.1016/j.berh.2011.01.005

Häuser, W., Jung, E., Erbslöh-Möller, B., Gesmann, M., Kühn-Becker, H., Petermann, F., … Wolfe, F. (2012). Validation of the fibromyalgia survey questionnaire within a cross-sectional survey. *PLoS ONE*, *7*(5), 3–8. https://doi.org/10.1371/journal.pone.0037504

Hoff, A. L., Palermo, T. M., Schluchter, M., Zebracki, K., & Drotar, D. (2006). Longitudinal relationships of depressive symptoms to pain intensity and functional disability among children with disease-related pain. *Journal of Pediatric Psychology*, *31*(10), 1046–1056. https://doi.org/jsj076 [pii]

Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary Care Companion for CNS Disorders*, *13*(2), 10.4088/PCC.10m01063. https://doi.org/10.4088/PCC.10m01063 [doi]

Karafin, M. S., Singavi, A., Hussain, J., Wandersee, N., Heinrich, T., Hurley, R. W., … Field, J. J. (2018). Predictive factors of daily opioid use and quality of life in adults with sickle cell disease. *Hematology*, *8454*(May), 1–8. https://doi.org/10.1080/10245332.2018.1479997

Keller, S., Yang, M., Treadwell, M. J., & Hassell, K. L. (2017). Sensitivity of alternative measures of functioning and wellbeing for adults with sickle cell disease: comparison of PROMIS(R) to ASCQ-Me. *Health and Quality of Life Outcomes*, *15*(1), 115–117. https://doi.org/10.1186/s12955-017-0661-5 [doi]

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2018). Estimating the Frequency , Severity , and Clustering of SPADE Symptoms in Chronic Painful Chemotherapy- Induced Peripheral Neuropathy. *Pain Management Nursing*, *19*(4), 354–365. https://doi.org/10.1016/j.pmn.2018.01.001

Kratz, A. L., Schilling, S. G., Goesling, J., & Williams, D. A. (2015). Development and Initial Validation of a Brief Self-Report Measure of Cognitive Dysfunction in Fibromyalgia. *The Journal of Pain*, *16*(6), 527–536. https://doi.org/10.1016/j.jpain.2015.02.008

Kroenke, K., Yu, Z., Wu, J., Kean, J., & Monahan, P. O. (2014). Operating characteristics of PROMIS four-item depression and anxiety scales in primary care patients with chronic pain. *Pain Medicine (Malden, Mass.)*, *15*(11), 1892–1901. https://doi.org/10.1111/pme.12537

Laurence, B., George, D., Woods, D., & Baltimore, D. (2006). *Association between Elevated*

Depressive Symptoms and Clinical Disease Severity in African-American Adults with Sickle Cell Disease.

Levenson, J. L., McClish, D. K., Dahman, B. A., Bovbjerg, V. E., De A. Citero, V., Penberthy, L. T., … Smith, W. R. (2008). Depression and anxiety in adults with sickle cell disease: The PiSCES project. *Psychosomatic Medicine*, *70*(2), 192–196. https://doi.org/10.1097/PSY.0b013e31815ff5c5

Maletic, V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Frontiers in Bioscience*, *14*, 5291–5338.

Mann-Jiles, V., Thompson, K., & Lester, J. (2015). Sleep impairment and insomnia in sickle cell disease: A retrospective chart review of clinical and psychological indicators. *Journal of the American Association of Nurse Practitioners*, *27*(8), 441–449. https://doi.org/10.1002/2327-6924.12212

McCabe, S. E., West, B. T., & Boyd, C. J. (2013). Motives for medical misuse of prescription opioids among adolescents. *The Journal of Pain : Official Journal of the American Pain Society*, *14*(10), 1208–1216. https://doi.org/10.1016/j.jpain.2013.05.004

McClish, D. K., Smith, W. R., Dahman, B. A., Levenson, J. L., Roberts, J. D., Penberthy, L. T., … Bovbjerg, V. E. (2009). Pain site frequency and location in sickle cell disease: The PiSCES project. *Pain*, *145*(1–2), 246–251. https://doi.org/10.1016/j.pain.2009.06.029

Merriwether, E. N., Barbara, A., Zimmerman, M. B., Dailey, D. L., Vance, C. G. T., Darghosian, L., … Chimenti, R. (2017). Reliability and Construct Validity of the Patient- Reported Outcomes Measurement Information System (PROMIS) Instruments in Women with Fibromyalgia. *Pain Medicine*, *18*, 1485–1495. https://doi.org/10.1093/pm/pnw187

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Moscou-Jackson, Gyasi, Finan, P. H., Campbell, C. M., & Smyth, Joshua M., Haythornthwaite, J. A. (2016). The Effect of Sleep Continuity on Pain in Adults with Sickle Cell Disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010.The

Moscou-Jackson, G., Finan, P. H., Campbell, C. M., Smyth, J. M., & Haythornthwaite, J. A. (2015). The effect of sleep continuity on pain in adults with sickle cell disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010

National Heart, Lung, and B. I. (2014). *Evidence-Based Management of Sickle Cell Disease: Expert Panel, 2014*. https://doi.org/10.1542/peds.2014-2986

Neville, S. J., Clauw, A. D., Moser, S. E., Urquhart, A. G., Clauw, D. J., Brummett, C. M., & Harte, S. E. (2018). Association between the 2011 Fibromyalgia Survey Criteria and Multisite Pain Sensitivity in Knee Osteoarthritis. *Clinical Journal of Pain*, *34*(10), 909–917. https://doi.org/10.1097/AJP.0000000000000619

Ochsner, K. N., Ludlow, D. H., Knierim, K., Hanelin, J., Ramachandran, T., Glover, G. C., & Mackey, S. C. (2006). Neural correlates of individual differences in pain-related fear and

anxiety. *Pain*, *120*(1–2), 69–77. https://doi.org/10.1016/j.pain.2005.10.014

Ozer, C., Yengil, E., Acipayam, C., & Kokacya, M. H. (2014). Relationship between depression, anxiety, quality of life and vaso-occlusive crisis in adolescents with sickle cell disease. *Acta Medica Mediterranea*, *30*(2), 335–339. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84898471979&partnerID=40&md5=7d617897f2596c49705119a3d2b85bcf

Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states--maybe it is all in their head. *Best Practice & Research.Clinical Rheumatology*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005 [doi]

Platt, O. S., Thorington, B. D., Brambilla, D. J., Milner, P. F., Rosse, W. F., Vichinsky, E., & Kinney, T. R. (1991). Pain in sickle cell disease. Rates and risk factors. *The New England Journal of Medicine*, *325*(1), 11–16. https://doi.org/10.1056/NEJM199107043250103 [doi]

PROMIS Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS) (Version 1.1.v 9). (n.d.). Retrieved from http://www.nihpromis.org

Schaible, H.-G. (2014). Nociceptive neurons detect cytokines in arthritis. *Arthritis Research & Therapy*, *16*(5), 470.

Sharma, S., Efi, J. T., Knupp, C., Kadali, R., Liles, D., & Shiue, K. (2015). Sleep Disorders in Adult Sickle Cell Patients, *11*(3), 1–5.

Shattuck, E. C., & Muehlenbein, M. P. (2016). Towards an integrative picture of human sickness behavior. *Brain, Behavior, and Immunity*, *57*, 255–262. https://doi.org/10.1016/j.bbi.2016.05.002

Sil, S., Cohen, L. L., & Dampier, C. (2016). Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *The Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289 [doi]

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., McClish, D. K., Roberts, J. D., Dahman, B., … Roseff, S. D. (2008). Daily assessment of pain in adults with sickle cell disease. *Annals of Internal Medicine*, *148*(2), 94–101. https://doi.org/148/2/94 [pii]

Spinhoven, P., Penninx, B. W., Hickendorff, M., van Hemert, A. M., Bernstein, D. P., & Elzinga, B. M. (2014). Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. *Psychological Assessment*, *26*(3), 717–729. https://doi.org/10.1037/pas0000002

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D. B., & Paulus, M. P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry*, *65*(11), 1275–1284. https://doi.org/10.1001/archpsyc.65.11.1275

Vacca Jr, V. M., & Blank, L. (2017). Sickle cell disease: Where are we now? *Nursing*, *47*(4), 26–34. https://doi.org/10.1097/01.NURSE.0000513609.79270.74 [doi]

Vitiello, M. V, Rybarczyk, B., Von Korff, M., & Stepanski, E. J. (2009). Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine*, *5*(4), 355–362.

Voepel-Lewis, T., Wagner, D., & Tait, A. R. (2015). Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. *JAMA Pediatrics*, *169*(5), 497–498. https://doi.org/10.1001/jamapediatrics.2014.3583

Wakefield, E. O., Popp, J. M., Dale, L. P., Santanelli, J. P., Pantaleao, A., & Zempsky, W. T. (2017). Perceived Racial Bias and Health-Related Stigma Among Youth with Sickle Cell Disease. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *38*(2), 129–134. https://doi.org/10.1097/DBP.0000000000000381 [doi]

Wallen, G. R., Minniti, C. P., Krumlauf, M., Eckes, E., Allen, D., Oguhebe, A., … Taylor, J. G. (2014). Sleep disturbance, depression and pain in adults with sickle cell disease. *BMC Psychiatry*, *14*, 207. https://doi.org/10.1186/1471-244X-14-207

Williams, D. A. (2018). Phenotypic features of central sensitization. *Journal of Applied Biobehavioral Research*, *23*(2), 1–15. https://doi.org/10.1111/jabr.12135

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., … Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism*, *46*(3), 319–329. https://doi.org/10.1016/j.semarthrit.2016.08.012

Zempsky, W T, Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread Pain Among Youth With Sickle Cell Disease Hospitalized With Vasoocclusive Pain: A Different Clinical Phenotype? *The Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403 [doi]

Zempsky, William T., Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread pain among youth with sickle cell disease hospitalized with vasoocclusive pain. *Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403

Zempsky, William T. (2009). Treatment of sickle cell pain: fostering trust and justice. *JAMA*, *302*(22), 2479–2480. https://doi.org/10.1001/jama.2009.1811

CHAPTER IV

Centralized Pain and Pain Catastrophizing as Predictors of Opioid Consumption and Pain Interference

Abstract

Introduction: Empirical evidence suggests that a subset of patients with SCD have centralized pain. Research among other centralized pain populations suggests that many patients with centralized pain consume more opioids due to opioid non-responsiveness. Further, individual patient factors like pain catastrophizing have been associated with opioid use and misuse. Limited research has evaluated the impact that centralized pain and pain catastrophizing have on opioid consumption and pain interference among adolescents and young adults with SCD

Purpose: The purpose of this prospective, predictive study was to 1) describe baseline centralized pain and pain catastrophizing among adolescents and young adults with SCD, and 2) evaluate the predictive relationships among baseline centralized pain, pain catastrophizing, and two primary outcome variables—opioid consumption and pain interference one month post-baseline.

Patients and Methods: Forty-eight adolescents and young adults completed baseline measures of centralized pain and pain catastrophizing. After baseline, participants received weekly text messages which included pain interference and opioid consumption surveys. Multi-predictor

two-part models were used to evaluate the predictive relationships among baseline variables, pain interference, and opioid consumption.

Results: Forty-eight adolescents and young adults aged 14-35 ($\bar{X}$=22.8; *SD*=5.9) completed baseline measures of centralized pain and pain catastrophizing. Thirty-three participants completed longitudinal measures of opioid consumption and pain interference throughout the one month study period. Twenty-five percent of our sample (*n*=12) had a centralized pain score ≥ 13 on the 2011 ACR Fibromyalgia Survey Criteria, indicating positive centralized pain. Centralized pain significantly increased the odds of consuming opioids (*OR*=1.2) and having pain interference (*OR*=1.46). Further, baseline centralized pain was significantly predictive of opioid consumption (β=0.13) and pain interference (β=0.05). The average marginal effects of centralized pain on opioid consumption and pain interference were 4.06 and 1.05, respectively. Thus, as centralized pain scores increased, average daily opioid consumption increased by 4.06 MME and pain interference scores increased by 1.05 points. Pain catastrophizing scores ranged from 0-50, with a mean severity of 16.23 (*SD*=13.36). Contrary to our hypothesis, pain catastrophizing scores significantly predicted less opioid consumption (β=-0.03). Further, pain catastrophizing scores had an average marginal effect of -0.77 on average daily opioid consumption MME. In the pain interference model, higher pain catastrophizing scores significantly increased the odds of having pain interference (*OR*=1.05). However, pain catastrophizing scores did not significantly predict longitudinal pain interference in the subset of patients (*n*=40) that had pain interference scores > 0.

Conclusion: Patients with centralized pain are at a greater risk of consuming opioids and more likely to experience pain that interferes with social, emotional, and physical function. Centralized pain can also predict opioid consumption and pain interference over time. Knowledge of the

presence of centralized pain can guide identification of high-risk patients and inform individualized pain management strategies. Overall, proper identification and management of centralized pain may reduce pain and opioid use and improve quality of life among patients with SCD.

Introduction

Acute pain, or vaso-occlusive pain crisis (VOC), is the most common reason for health service utilization among patients with sickle cell disease (SCD) (Platt et al., 1991; Vacca Jr & Blank, 2017). Despite the impact of pain and health service use among these patients, limited pharmacologic and non-pharmacologic interventions have a limited effect in managing daily pain (Wally R Smith et al., 2008). Research among other pain populations has identified two clinical characteristics, centralized pain and pain catastrophizing, among others, that may predict daily pain, and opioid response and use (K Phillips & Clauw, 2013; Kristine Phillips & Clauw, 201; M O Martel et al., 2013; Marc O Martel et al., 2014; Morasco, Turk, Donovan, & Dobscha, 2013).

First, centralized pain is pain that arises from altered nociception with minimal or no tissue damage or evidence for disease or lesion of the somatosensory system (Latremoliere & Woolf, 2009; Marchand, 2008; Woolf, 2011). Patients with centralized pain often present clinically with widespread pain, increased pain sensitivity, reduced physical function, and opioid non-responsiveness (K Phillips & Clauw, 2013; Kristine Phillips & Clauw, 2011). Opioid non-responsiveness is a lack of pain relief or increased pain intensity after opioid use, leading to increased opioid consumption (Brummett et al., 2013; Corli et al., 2017; Hanks & Forbes, 1997; Janda et al., 2015; Wasserman et al., 2014). Empirical evidence suggests patients with SCD who receive chronic opioid therapy present with many centralized pain manifestations—increased

pain hyperalgesia, temperature sensitivity, and depressive symptoms and reduced function (C. P. Carroll et al., 2016b). However, the presence of centralized pain and the associated risk of opioid non-responsiveness is generally not considered by clinicians when prescribing analgesics. Thus, there is a clinical need to determine which individuals with SCD have centralized pain and consequently may be more susceptible to opioid misuse.

In addition to opioid non-responsiveness, a growing body of literature describes patterns and personal factors that are linked to opioid use and misuse among patients with chronic or centralized pain (Grattan, Sullivan, Saunders, Campbell, & Von Korff, 2012; Jamison, Serraillier, & Michna, 2011; M O Martel et al., 2013; Marc O Martel et al., 2014). Several studies have found associations between pain catastrophizing and opioid misuse among patients with chronic pain (M O Martel et al., 2013; Marc O Martel et al., 2014; Morasco et al., 2013). Catastrophizing occurs when a patient has irrational thoughts about their pain including rumination, magnification and helplessness (Citero et al., 2007; Quartana, Campbell, & Edwards, 2009). Pain catastrophizing is often described as an exaggerated, negative cognitive-affective response to current or anticipated pain and has been associated with increased pain sensitivity and severity among patients with SCD (N Bakshi et al., 2017; Graves & Jacob, 2014). However, there is a paucity of literature that has evaluated the relationship between pain catastrophizing and opioid use within the SCD population (Patrick H Finan et al., 2018).

In summary, there are gaps in the literature regarding the relationships among centralized pain, pain catastrophizing, opioid consumption, and pain interference. To address these gaps, we used prospective, predictive study design and aimed to 1) describe the incidence and severity of baseline centralized pain and pain catastrophizing, and 2) evaluate the predictive relationships among baseline centralized pain and pain catastrophizing severity, weekly opioid consumption,

and pain interference within one month of baseline phenotyping. The overarching hypothesis of this study was that baseline centralized pain severity and pain catastrophizing severity would predict average daily opioid consumption (MME) and weekly pain interference one month post-baseline in adolescents and young adults with SCD.

Methods

Sample and Setting

Adolescents and adults with SCD (*N*=48) were recruited between 8/2019-12/2020 from the Pediatric and Adult Comprehensive Sickle Cell Clinics at Mott Children's Hospital and Michigan Medicine. Patients were included in the study if they were between the ages of 14 and 35 and could speak and read English. Patients were excluded from the study if they did not own a smartphone. The study was approved by the University of Michigan Institutional Review Board.

Recruitment and Data Collection

Recruitment and baseline data collection procedures were previously described in Chapter III. Briefly, potentially eligible patients were pre-screened via chart review and discussion with clinic providers. The PI or trained research assistant discussed study procedures, obtained informed consent, and collected baseline data with all study participants during their outpatient clinic appointment. Two participants who did not have an upcoming outpatient appointment met with the PI or trained research assistant outside of clinic to provide informed consent and complete baseline data.

To address the study aims, participants completed electronic Qualtrics™ surveys assessing the sample's demographic characteristics, centralized pain, pain catastrophizing, opioid consumption, and pain interference. The survey order was randomized via the randomizer

element within Qualtrics™. Following survey completion, the PI or research assistant instructed participants on how to download the GeoPain @ Home mobile application (app) on their personal cell phone. Participants were instructed on how to use the app and completed their baseline data.

After baseline, participants were instructed to complete the body map in the GeoPain @ Home app every day for 30 days. Daily reminders were enabled within the app so that participants received a notification every day to fill out the body map. To collect longitudinal pain interference and opioid consumption information, participants received a Qualtrics™ SMS text message containing a link to the pain interference and opioid consumption surveys every Friday for 30 days (four times total).

Measures

Demographic Survey. Participants self-reported their age, gender, education level, and sickle cell genotype within the baseline demographic survey. Sickle cell genotype was confirmed in the electronic medical record (EMR) by the PI or research assistant.

ACR 2011 Fibromyalgia Survey Criteria. The ACR 2011 Fibromyalgia Survey Criteria was used to evaluate the degree of centralized pain (Wolfe et al., 2016). The survey contains two subscales, 1) the Widespread Pain Index (WPI) (19 items) evaluating the presence or absence of pain over the last 7 days in 19 different body regions, and 2) the Symptom Severity Scale (SSS) (6 items) evaluating the severity and presence of six comorbid symptoms. Scores from the WPI and the SSS are summed to create a total survey score ranging from 0-31 (Wolfe et al., 2016). Empirical evidence supports the measure's internal consistency reliability (α=0.71), validity (content and convergent), and responsiveness (Häuser et al., 2012; Neville et al., 2018; Wolfe et al., 2016). Further, evaluations of ACR 2011 Fibromyalgia Survey Criteria's sensitivity and

specificity support the measure's ability to identify criteria positive patients, or those with centralized pain (Wolfe et al., 2016).

Pain Catastrophizing Scale. The Likert-type Pain Catastrophizing Scale (PCS) assess thoughts and feelings about pain within 13-items (Sullivan, Bishop, & Pivik, 1995). Total PCS scores range from 0 to 52 with higher scores indicative of greater catastrophic thinking about pain. The PCS has demonstrated strong internal reliability ($\alpha = 0.93$), convergent and discriminant validity, and structural validity based on confirmatory factor analysis results (Osman et al., 1997).

PROMIS® Short Form v1.0 – Pain Interference 4a. The 8-item PROMIS® Pain Interference Short Form assesses the self-reported consequences of pain on social, cognitive, emotional, physical, and recreational activities over the previous 7 days using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating more activity interference due to pain (Cella et al., 2010). Previous psychometric testing of the PROMIS® Pain Interference Short Form supports the measures' internal consistency reliability ($\alpha = 0.90$ to 0.99), test-retest reliability (ICC 0.83 to 0.95), and sensitivity in adolescents and adults with centralized pain (Amtmann et al., 2010; Broderick et al., 2013).

Opioid Consumption. Participants self-reported which, if any, opioids they were taking, and the average number of pills taken per day within the previous seven days within the Qualtrics™ Opioid Consumption survey. The average number of pills taken per day were converted into average daily milligram morphine equivalents (MME) using the Oregon Pain Guidance Opioid Conversion Calculator (2017). Participants completed the Opioid Consumption survey at baseline and every Friday for 30 days (four times total).

GeoPain @ Home Mobile Application. Daily pain intensity was included as a covariate within our predictive models. Participants reported daily pain intensity using a color scale from 0 to 10

within the GeoPain™ @ Home interactive body map (MoxyTech Inc., MI). After selecting their pain intensity, participants shaded the corresponding body area. If varying pain intensity was reported in different body regions, all intensity scores were averaged to derive an overall body map pain intensity score. Participants were instructed to complete a body map daily throughout the 30-day study period. Daily pain intensity scores were aggregated into an average weekly pain intensity score. Thus, each participant had one baseline pain intensity score and four average weekly pain intensity scores.

Statistical Analyses

Electronic survey and mobile application data were exported from Qualtrics™ and the GeoPain @ Home internet server and analyzed using Stata software (StataCorp, 2017). Descriptive statistics (e.g. means, frequencies, 95% confidence intervals, and standard deviations) were calculated for all variables and covariates including demographic characteristics, pain catastrophizing, centralized pain, pain intensity, opioid consumption MME, and pain interference. For all PROMIS® Pain Interference SF scores, the raw total scores were converted to T-scores (mean=50, standard deviation=10) using the PROMIS® Health Measures Scoring Service ("PROMIS® Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS®) (Version 1.1.v 9)").

The Oregon Pain Guidance Opioid Conversion Calculator (2017) was used to convert opioid use into average daily morphine milliequivalents (MME) based on Opioid Consumption Surveys and corresponding electronic medical record (EMR) dosages. We excluded one opioid consumption diary based on suspected entry error (700 MME). Six participants reported taking opioids that were discontinued. In these instances, average daily opioid consumption MME was calculated from the discontinued prescriptions. Further, three participants reported taking

codeine with no EMR prescription history. Since it is possible that these participants were prescribed opioids from outside institutions, we utilized standard-adult dosages of codeine/acetaminophen (30/300mg) from Chronic Pain Clinical Practice Guidelines to calculate average daily opioid consumption MME for these three participants (Michigan Medicine Clinical Care Guidelines, 2016).

To evaluate the predictive relationships among centralized pain, pain catastrophizing, and our two outcome variables, pain interference and opioid consumption, we ran a series of multi-predictor two-part models for mixed discrete-continuous outcomes. All models incorporated the nesting of observations within person due to the longitudinal experimental design (cluster-adjusted standard errors). Two-part models simultaneously use a logit model to predict the probability of a binary zero versus a positive outcome, and also an ordinary least squares regression model to predict the positive outcome (Belotti, Deb, Manning, & Norton, 2015). Since pain interference scores range from 8-40, with a score of 8 representing no pain interference, we rescaled the total scores with a range from 0-32. Using two-part models for our analyses allowed us to include all pain interference and opioid consumption data, including zero values. We evaluated the centrality and dispersion of pain interference and opioid consumption data with and without zero values. The distribution of each dependent variable was right skewed even when analyzing positive values. For this reason, we used ordinary least squares (OLS) linear regression models with logged non-zero dependent variables to predict the positive values within each two-part model. Since both our dependent variables were logged, we used a nonparametric smearing retransformation method, Duan's smearing retransformation, to produce interpretable fitted values of the two-part models (Duan, 1983). Consistent with Duan (1983), we

used nonparametric bootstrapping to re-estimate the model and re-compute the standard errors and confidence intervals (Belotti et al., 2015; Duan, 1983).

Age and sex were two demographic covariates included in the models. Additionally, to account for the effect of pain intensity on pain interference and opioid consumption, we included longitudinal pain intensity scores as a covariate within each model. Three participants were unable to download the GeoPain @ Home mobile app on their personal cell phone to provide baseline and longitudinal pain intensity data. Thus, baseline pain intensity scores were reported by 45 participants. After baseline, 34 participants completed a total of 746 daily body maps out of a possible 1440 (51.8% adherence). Baseline and average weekly pain intensity scores comprised 162 total pain intensity scores that were used in the predictive analyses.

Results

Demographics

Sample demographic information of all participants (*N*=48) is presented in Table 1. Briefly, participants had a mean age of 22.8 years (*SD*= 5.9; range: 14-35 years). The majority of the sample were female (56.4%), African American (97.9%), and non-Hispanic (97.9%). The most common sickle cell genotypes were HbSS (72.9%) and HbSC (20.8%).

Data Completion

All participants (*N*=48) completed baseline demographics pain catastrophizing, centralized pain, opioid consumption, and pain interference surveys. After baseline, participants were sent weekly pain interference and opioid consumption surveys via a Qualtrics™ SMS text message. Throughout the four-week study period, 33 participants completed 91 pain interference and 91 opioid consumption surveys (47.4% adherence).

Descriptive Statistics of Baseline Variables

Baseline centralized pain, pain catastrophizing, pain intensity, pain interference and opioid consumption descriptive statistics are provided in Table 2. Centralized pain scores ranged from 1 to 20 with an average score of 8.96 in our sample. A total of 12 participants (25%) had a centralized pain score ≥ 13, indicating positive centralized pain. Mean pain catastrophizing scores were relatively low ($\bar{X}$= 16.23), with a wide total score range from 0-50, with higher scores signifying greater catastrophic thinking about pain. However, 75% (*n*=36) of our sample, had total pain catastrophizing scores that were ≤ 25. At baseline, participants reported opioid consumption of 22.1 MME per day, on average. Baseline pain interference scores ranged from 41.6-75.6 with a mean score of 55.56.

Descriptive Statistics of Longitudinal Variables

Descriptive statistics of longitudinal daily opioid consumption MME and pain interference are provided within Table 3. Mean opioid consumption was 18.58 MME per day with a wide range of 0 to 150 MME. Pain Interference scores were about 0.5 standard deviations higher than the PROMIS® normative sample mean, on average. Lastly, average weekly pain intensity scores ($\bar{X}$= 2.56) were relatively low throughout the 30-day study period.

Opioid Consumption Model Results

Table 4 provides the results of the two-part model that evaluated the predictive relationships among centralized pain, pain catastrophizing, and average daily opioid consumption MME. Higher centralized pain scores increased the odds of consuming opioids [Odds Ratio (*OR*)=1.2; 95% Confidence Interval (*CI*)= 1.04 – 1.38]. In the sample that consumed opioids (*n*=30), centralized pain scores predicted higher opioid consumption (β=0.13;

CI = 0.08 – 0.19). Pain catastrophizing scores did not significantly increase the odds of consuming opioids (OR= 0.99; *CI* = 0.94 – 1.05). In the sample that consumed opioids (*n*=30), pain catastrophizing scores significantly predicted less opioid consumption (β=-0.03; *CI* = -0.06 – -0.01).

Table 5 provides the average marginal effects for each independent variable on average daily MME for the combined two-part model. Both effects were significant at the 5% level. The marginal effect of centralized pain on average daily MME is depicted in Figure 5. As centralized pain scores increased, opioid consumption increased by 4.06 MME while controlling for age, sex, pain intensity, and pain catastrophizing. As pain catastrophizing scores increased, opioid consumption decreased by -0.77 MME while controlling for age, sex, pain intensity, and centralized pain.

Pain Interference Model Results

Table 6 includes the results of the two-part model which evaluated the predictive relationships among the independent variables and longitudinal pain interference scores. Similar to the opioid consumption model, higher centralized pain scores significantly increased the odds of having pain interference (*OR*=1.46; *CI* = 1.21 – 1.76). In the subset of patients with pain interference scores >0 (*n*=40), baseline centralized pain scores were positively and significantly predictive of longitudinal pain interference (β=0.06; *CI* = 0.02 – 0.21). Higher pain catastrophizing scores significantly increased the odds of having pain interference (*OR*=1.05; *CI* = 1.01 – 1.1). However, pain catastrophizing scores did significantly predict longitudinal pain interference in the sample that had pain interference scores > 0 (*n*=40).

Average marginal effects of centralized pain and pain catastrophizing on pain interference are provided in Table 7. Age, gender, and pain intensity were all controlled for when calculating average marginal effects of centralized pain and pain catastrophizing on pain interference. Centralized pain had a significant marginal effect of 1.05 on pain interference (Figure 6). As centralized pain scores increased, pain interference scores also increased by 1.05. Pain catastrophizing did not have significant average marginal effect on pain interference.

Discussion

In this study we aimed to 1) describe the incidence and severity of baseline centralized pain and pain catastrophizing, and 2) evaluate the predictive relationships of baseline predictors (i.e., centralized pain and pain catastrophizing) on average daily opioid consumption and weekly pain interference within one month of baseline phenotyping.

Twenty-five percent of the participants in our study were positive for centralized pain based on the ACR 2011 Fibromyalgia Survey Criteria. This percentage is comparable with other research studies that have evaluated centralized pain among patients with SCD (Amanda M. Brandow et al., 2013; C. M. Campbell et al., 2016; M O Ezenwa et al., 2015; Eufemia Jacob et al., 2015). Further, this study found significant and positive predictive relationships between centralized pain and two primary outcomes—opioid consumption and pain interference. The positive relationship found between centralized pain and opioid consumption is supported in the literature (Brummett et al., 2013; Janda et al., 2015). Patients and clinicians frequently increase opioid dosages when an opioid is ineffective in managing pain, which consequently results in opioid non-responsiveness (Brummett et al., 2013; Hanks & Forbes, 1997; Janda et al., 2015; Wasserman et al., 2014).

Despite the evidence suggesting opioid non-responsiveness in the centralized pain population (Corli et al., 2017; Hanks & Forbes, 1997; Wasserman et al., 2014), centralized pain is rarely considered when managing daily pain in the SCD population. Many studies conducted among patients with SCD have identified patients with and without centralized pain using quantitative sensory testing (QST) (C. M. Campbell et al., 2016; C. P. Carroll et al., 2016a; Eufemia Jacob et al., 2015). Although evidence supports the strong psychometric properties of QST methods, their use and feasibility within clinical and research settings is limited due to equipment costs, administration time, and extensive training requirements (Rolke et al., 2006).

To our knowledge, our study is the first to evaluate centralized pain among patients with SCD using a patient-reported outcome (PRO) measure, the ACR 2011 Fibromyalgia Survey Criteria. As an alternative to QST, administering this PRO measure in clinical or research settings is convenient and feasible. Further, empirical evidence supports the sensitivity and specificity of the survey to differentiate those with and without centralized pain (Wolfe et al., 2016). The ACR 2011 Fibromyalgia Survey Criteria could be useful to identify patients within clinical settings who may be at an increased risk for consuming more opioids and having more pain interference. Ultimately, measuring centralized pain in the clinical setting may facilitate individualized pain management including referrals to specialists (e.g., integrative health practitioners, palliative care providers) and the use of non-pharmacologic pain management approaches over ineffective pharmacologic therapies (opioids).

The findings of our study also have implications for non-pharmacologic pain management approaches for SCD-associated pain. Empirical evidence supports the efficacy of non-pharmacologic pain management approaches for centralized pain (Eller-smith et al., 2018; Hassett & Williams, 2011). To our knowledge, only five randomized control trials (RCTs)

conducted among patients with SCD have tested the efficacy of non-pharmacologic interventions including yoga, massage, relaxation, healing touch, and CBT (L P Barakat et al., 2010; Miriam O. Ezenwa et al., 2016; Lemanek et al., 2009; Moody et al., 2017; Schatz et al., 2015; Thomas et al., 2013). However, all five RCTs had either no or minimal effect on daily pain.

There is a growing body of evidence supporting the effectiveness of cognitive behavioral therapy (CBT) to reduce pain and improve function in non-SCD centralized pain populations (Eller-smith et al., 2018; Hassett & Williams, 2011; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). Cognitive behavioral therapy refers to a wide variety of interventions such as progressive muscle relaxation, hypnosis, guided visual imagery, and coping skills training (R Knoerl, Lavoie Smith, & Weisberg, 2015). There are several different mechanisms that may contribute to CBT efficacy (Eller-smith et al., 2018; Seminowicz et al., 2013). For example, CBT interventions have been associated with an increase in gray matter within pain processing areas of the brain including the subgenual anterior cingulate, sensorimotor, and prefrontal and posterior parietal cortices, as well as hippocampus (Seminowicz et al., 2013). An increase in gray matter within many of these areas has been associated with changes in pain perception and thoughts related to pain (e.g., decreased pain catastrophizing) (Seminowicz et al., 2013).

Two of the non-pharmacologic RCTs conducted among patients with SCD have investigated the efficacy of CBT-based interventions (Lamia P. Barakat, Schwartz, Salamon, & Radcliffe, 2010; Schatz et al., 2015). Despite the established benefit of CBT in other centralized pain populations, these studies had either no or minimal effects in reducing pain (Lamia P. Barakat et al., 2010; Schatz et al., 2015). Minimal effects within these studies may be due to internal validity threats (i.e., small sample sizes, no participant blinding, lack of intervention

standardization). Future non-pharmacologic intervention studies are needed to evaluate the effectiveness of CBT among patients with SCD.

Baseline pain catastrophizing scores were relatively low in our sample. Average scores pain catastrophizing scale (PCS) scores were 16.23; previous literature has reported much higher mean PCS scores ($\bar{X}$= 28.5-29) among patients with SCD (N Bakshi et al., 2017). In contrast to our hypothesis, pain catastrophizing significantly predicted less opioid use. These findings conflict with research supporting a predictive relationship between pain catastrophizing and increased opioid consumption in SCD populations (Patrick H Finan et al., 2018; M O Martel et al., 2013; Morasco et al., 2013). These conflicting findings may be explained by the overall low pain catastrophizing scores within our sample, as previously described. Total PCS scores can range from 0-52. However, 75% of our sample had total PCS scores ≤ 25.

Low mean pain catastrophizing in our study may be explained by recall bias, or an inability to accurately remember previous events (Gendreau, Hufford, & Stone, 2003). The PCS asks respondents to recall their thoughts about pain from a previous painful event (Sullivan et al., 1995). Empirical evidence suggests that emotional processes may bias the ability to recall past negative events (Chan, Goodwin, & Harmer, 2007; Gendreau et al., 2003; Leppanen, 2006). Further, the ability to recall a past painful event may have been confounded by relatively low pain intensity scores within our sample. Many participants within our sample reported either no or minimal daily pain throughout the study period. These participants may have had difficulty accurately recalling a previous painful event and responding to the questions within the PCS. In summary, low mean pain catastrophizing due to recall bias may have limited the ability of our statistical model to accurately predict the relationships among pain catastrophizing, opioid consumption and pain interference.

Our conflicting findings may also be explained by the way pain catastrophizing was measured. The PCS evaluates dispositional pain catastrophizing or the trait-like tendency of catastrophic thinking. Empirical evidence suggests that measuring situational pain catastrophizing, immediately following a painful event, may be more appropriate among patients who experience daily pain (C. M. Campbell, Kronfli, et al., 2011; Edwards, Campbell, & Fillingim, 2005). Prior research among patients with centralized pain compared measures of dispositional and situational pain catastrophizing and suggests that situational pain catastrophizing has a much stronger association with experimental pain responses (C. M. Campbell, Kronfli, et al., 2011). Thus, the results of our predictive models may have supported our hypothesis if we had measured situational catastrophizing at multiple time points throughout the study period.

Our research study has several limitations. First, low pain catastrophizing severity and potential recall bias during baseline survey completion may have limited our ability to accurately predict the relationships among pain catastrophizing, opioid consumption and pain interference. Second, although the statistical modeling procedures used within this study were appropriate based on the distribution of our data, our findings should be interpreted with caution due to our small sample size. Further, many patients did not adhere to completing weekly opioid consumption and pain interference surveys. Fifteen participants did not complete any opioid consumption or pain interference surveys after baseline. These missing data may have biased the findings of our study and reduced the representativeness of our sample. Our study is also limited by the discrepancies found in our self-reported opioid consumption data. One baseline self-reported opioid consumption diary was excluded from our analyses due to a suspected entry error of 700 MME. Also, a number of participants reported taking opioid prescriptions that were either

discontinued or absent from the EMR. The discrepancies in self-reported opioid consumption may be suggestive of recall bias which may have confounded our results. Lastly, our study only included patients from one academic medical center, limiting the generalizability of our findings to all patients with SCD.

In conclusion, our findings did not support positive relationships among pain catastrophizing, opioid consumption, and pain interference. These findings should be interpreted with caution due to suspected recall bias and low variability of pain catastrophizing severity within our sample. Our study also found that the centralized pain is associated with increased opioid consumption. Evaluating centralized pain in clinical and research settings—perhaps with the ACR 2011 Fibromyalgia Survey—is vital to guide individualized pain management. Clinicians may use centralized pain assessments to identify those who are at an increased risk for consuming more opioids and having pain that interferes with social, emotional, and physical function. Ultimately, clinical awareness of centralized pain may reduce daily pain and ineffective opioid use and improve functioning among patients with SCD.

TABLE 6

Demographic Characteristics, N=48

Variable	*N (%)*
Age	
Mean (SD)	22.8 (5.9)
Range	14-35
Sex	
Female	27 (56.4)
Male	21 (43.8)
Race	
African American	47 (97.9)
More than one race	1 (2.1)
Ethnicity	
Not Hispanic or Latino	47 (97.9)
Unknown or do not wish to report	1 (2.1)
Education	
In middle school	1 (2.1)
In high school	11 (22.9)
Did not complete high school	3 (6.3)
Completed high school	4 (8.3)
Some college or technical training	16 (33.3)
University undergraduate degree	12 (25)
University post graduate degree	1 (2.1)
Sickle Cell Genotype	
HbSS	35 (72.9)
HbSC	10 (20.8)
HbSβ0	1 (2.1)
HbSβ+	2 (4.2)

Table 7

Descriptive Statistics of Baseline Variables, N=48

Variable	*Mean*	*SD*	*Minimum*	*Maximum*
Pain Catastrophizing	16.23	13.36	0	50
ACR 2011 FM Survey Criteria	8.96	5.26	1	20
Opioid Consumption MME+	22.1	42.58	0	246
PROMIS® Pain Interference SF	55.56	10.91	41.6	75.6
Pain Intensity	3.41	2.57	0	9.71

Note. SD=standard deviation; FM=Fibromyalgia; MME=Morphine Milliequivalents; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=Short Form; +Outlier excluded (*n*=47)

Table 8

Descriptive Statistics of Longitudinal Variables

Variable	Obs	Mean	SD	Minimum	Maximum
Opioid Consumption MME	91	18.58	5.37	0	150
PROMIS® Pain Interference SF	91	54.45	1.28	40.7	77
Average Weekly Pain Intensity	117	2.56	0.33	0	7.8

Note. Obs=number of observations; SD=standard deviation; FM=Fibromyalgia; MME= Morphine Milliequivalents; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=Short Form

Table 9

Two-part model of pain catastrophizing and centralized pain on average daily opioid consumption MME

Variables	**Two-part model**	
	Logit	**OLS**
	Odds Ratio *(S.E.)* [a]	*Coefficients* *(S.E.)* [a]
Pain Catastrophizing	0.99 (0.03)	-0.03* (0.01)
Centralized Pain	1.20* (0.09)	0.13* (0.03)

Note. MME= Morphine Milliequivalents; OLS= ordinary least squares; S.E.= standard error; OLS regression model was conditional non-zero outcome; [a] Shows the cluster-robust standard errors; *p <0.05

Table 10

Average marginal effects for pain catastrophizing and centralized pain on average daily opioid consumption for combined two-part model

Variables	*Observed Coefficients*[a]	*Std Error*[b]	*Z Value*	*p Value*	*95% C.I.*[b]	
					Lower Limit	*Upper Limit*
Pain Catastrophizing	-0.77	0.35	-2.24	0.03	-1.45	-0.1
Centralized Pain	4.06	0.99	4.08	<0.00	2.11	6.01

[a] Duan smearing retransformation was used to obtain fitted values; [b] Nonparametric bootstrapping was used to calculate standard errors and confidence intervals; Controlling for age, gender, and pain intensity

Table 11

Two-part model of pain catastrophizing and centralized pain on weekly pain interference

Variables	**Two-part model**	
	Logit	**OLS**
	Odds Ratio *(S.E.)* [a]	*Coefficients* *(S.E.)* [a]
Pain Catastrophizing	1.05* (0.02)	-0.001 (0.01)
Centralized Pain	1.46* (0.14)	0.06* (0.02)

Note. OLS= ordinary least squares; S.E.= standard error; OLS regression model was conditional non-zero outcome; [a] Shows the cluster-robust standard errors; *p <0.05

Table 12

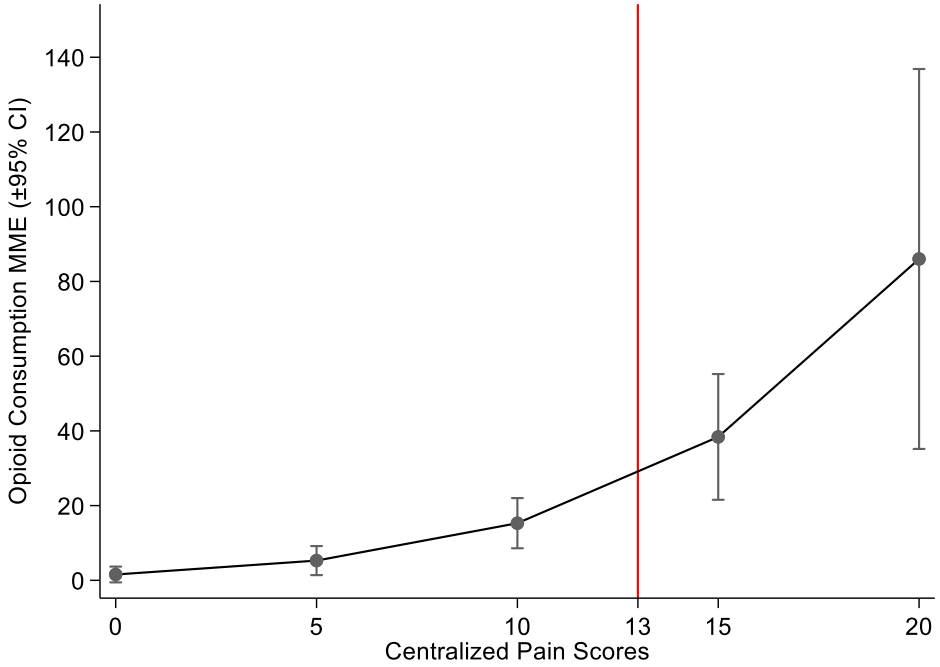
Marginal effects of pain catastrophizing and centralized pain on weekly pain interference for combined two-part model

Variables	*Observed Coefficients*[a]	*Std Error*[b]	*Z Value*	*p Value*	*95% C.I.*[b]	
					Lower Limit	*Upper Limit*
Pain Catastrophizing	0.03	0.09	0.38	0.70	-0.14	0.20
Centralized Pain	1.05	0.28	3.78	<0.00	0.51	1.60

[a] Duan smearing retransformation was used to obtain fitted values; [b] Nonparametric bootstrapping was used to calculate standard errors and confidence intervals; Controlling for age, gender, and pain intensity

Figure 5

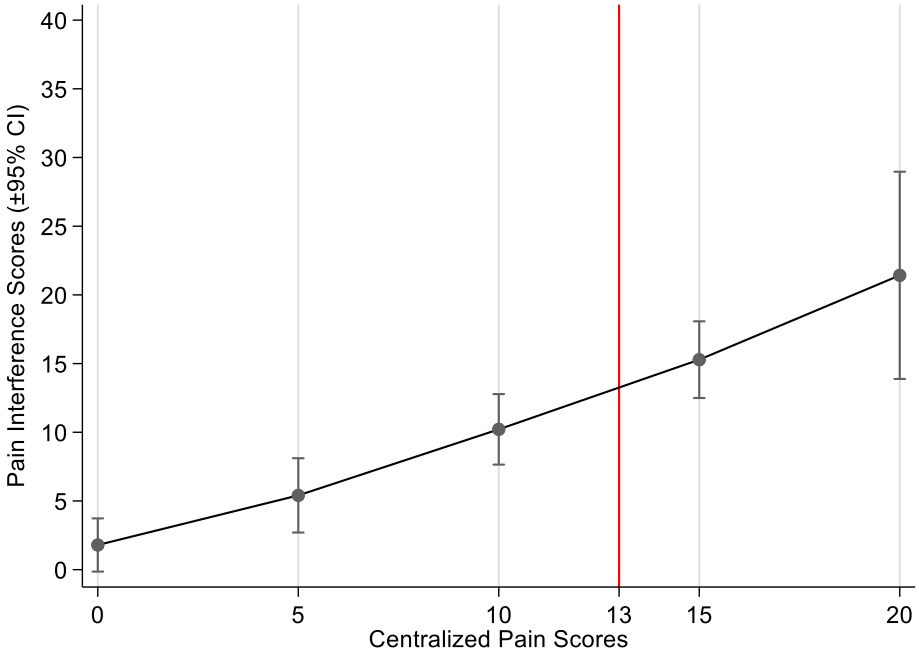
Predictive margins of centralized pain on average daily opioid consumption MME



Note. A score of 13 on the ACR 2011 Fibromyalgia Survey is indicative of positive centralized pain

Figure 6

Predictive average marginal effects of centralized pain on weekly pain interference



Note. A score of 13 on the ACR 2011 Fibromyalgia Survey is indicative of positive centralized pain

References

Amtmann, D., Cook, K. F., Jensen, M. P., Chen, W. H., Choi, S., Revicki, D., … Lai, J. S. (2010). Development of a PROMIS item bank to measure pain interference. *Pain*, *150*(1), 173–182. https://doi.org/10.1016/j.pain.2010.04.025 [doi]

Bakshi, N., Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Barakat, L P, Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Barakat, Lamia P., Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Belotti, F., Deb, P., Manning, W. G., & Norton, E. C. (2015). twopm: Two-part models. *Stata Journal*, *15*(1), 3–20. https://doi.org/10.1177/1536867x1501500102

Brandow, A. M., Stucky, C. L., Hillery, C. A., Hoffmann, R. G., & Panepinto, J. A. (2013). Patients with sickle cell disease have increased sensitivity to cold and heat. *American Journal of Hematology*. https://doi.org/10.1002/ajh.23341

Broderick, J. E., Schneider, S., Junghaenel, D. U., Schwartz, J. E., & Stone, A. A. (2013). Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. *Arthritis Care & Research*, *65*(10), 1625–1633. https://doi.org/10.1002/acr.22025

Brummett, C. M., Janda, A. M., Schueller, C. M., Tsodikov, A., Morris, M., Williams, D. A., & Clauw, D. J. (2013). Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology*, *119*(6), 1434–1443. https://doi.org/10.1097/ALN.0b013e3182a8eb1f [doi]

Campbell, C. M., Kronfli, T., Buenaver, L. F., Smith, M. T., Haythornthwaite, J. A., & Edwards, R. R. (2011). Situational vs. dispositional measurement of catastrophizing: Associations. *J Pain*, *11*(5), 443–453. https://doi.org/10.1016/j.jpain.2009.08.009.Situational

Campbell, C. M., Moscou-Jackson, G., Carroll, C. P., Kiley, K., Haywood, C., Lanzkron, S., … Haythornthwaite, J. A. (2016). An Evaluation of Central Sensitization in Patients With Sickle Cell Disease. *The Journal of Pain*, *17*(5), 617–627. https://doi.org/10.1016/j.jpain.2016.01.475

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell

Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77. https://doi.org/10.1016/j.amepre.2016.02.012

Chan, S. W. Y., Goodwin, G. M., & Harmer, C. J. (2007). Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine*, *37*(9), 1281–1291. https://doi.org/10.1017/S0033291707000669

Citero, V. de A., Levenson, J. L., McClish, D. K., Bovbjerg, V. E., Cole, P. L., Dahman, B. A., … Smith, W. R. (2007). The role of catastrophizing in sickle cell disease - The PiSCES project. *Pain*, *133*(1–3), 39–46. https://doi.org/10.1016/j.pain.2007.02.008

Corli, O., Roberto, A., Bennett, M. I., Galli, F., Corsi, N., Rulli, E., & Antonione, R. (2017). Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Practice*. https://doi.org/10.1111/papr.12669 [doi]

Duan, N. (1983). Smearing Estimate: A Nonparametric Retransformation Method. *Journal of the American Statistical Association*, *78*(383), 605–610. https://doi.org/10.2307/2288126

Edwards, R. R., Campbell, C. M., & Fillingim, R. B. (2005). Catastrophizing and experimental pain sensitivity: only in vivo reports of catastrophic cognitions correlate with pain responses. *The Journal of Pain : Official Journal of the American Pain Society*, *6*(5), 338–339. https://doi.org/10.1016/j.jpain.2005.02.013

Eller-smith, O. C., Nicol, A. L., Christianson, J. A., & Barr, G. A. (2018). Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions, *12*(February), 1–18. https://doi.org/10.3389/fncel.2018.00035

Ezenwa, M O, Molokie, R. E., Wang, Z. J., Yao, Y., Suarez, M. L., Pullum, C., … Wilkie, D. J. (2015). Safety and Utility of Quantitative Sensory Testing among Adults with Sickle Cell Disease: Indicators of Neuropathic Pain? *Pain Practice*, *16*(3), 282–293. https://doi.org/10.1111/papr.12279

Ezenwa, Miriam O., Yao, Y., Engeland, C. G., Molokie, R. E., Wang, Z. J., Suarez, M. L., & Wilkie, D. J. (2016). A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *Journal of Advanced Nursing*, *72*(6), 1452–1463. https://doi.org/10.1111/jan.12895

Finan, P. H., Carroll, C. P., Moscou-Jackson, G., Martel, M. O., Campbell, C. M., Pressman, A., … Haythornthwaite, J. A. (2018). Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis. *The Journal of Pain*, *19*(1), 46–56. https://doi.org/10.1016/j.jpain.2017.08.010

Gendreau, M., Hufford, M. R., & Stone, A. A. (2003). Measuring clinical pain in chronic widespread pain: Selected methodological issues. *Best Practice and Research: Clinical*

Rheumatology, *17*(4), 575–592. https://doi.org/10.1016/S1521-6942(03)00031-7

Grattan, A., Sullivan, M. D., Saunders, K. W., Campbell, C. I., & Von Korff, M. R. (2012). Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Annals of Family Medicine*, *10*(4), 304–311. https://doi.org/10.1370/afm.1371

Graves, J. K., & Jacob, E. (2014). Pain, coping, and sleep in children and adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing*, *27*(3), 109–120. https://doi.org/10.1111/jcap.12077 [doi]

Hanks, G. W., & Forbes, K. (1997). Opioid responsiveness. *Acta Anaesthesiologica Scandinavica*, *41*(1 Pt 2), 154–158.

Hassett, A. L., & Williams, D. A. (2011). Non-pharmacological treatment of chronic widespread musculoskeletal pain. *Best Practice & Research. Clinical Rheumatology*, *25*(2), 299–309. https://doi.org/10.1016/j.berh.2011.01.005

Häuser, W., Jung, E., Erbslöh-Möller, B., Gesmann, M., Kühn-Becker, H., Petermann, F., … Wolfe, F. (2012). Validation of the fibromyalgia survey questionnaire within a cross-sectional survey. *PLoS ONE*, *7*(5), 3–8. https://doi.org/10.1371/journal.pone.0037504

Hofmann, S. G., Asnaani, A., Vonk, I. J. J., Sawyer, A. T., & Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognitive Therapy and Research*, *36*(5), 427–440. https://doi.org/10.1007/s10608-012-9476-1

Jacob, E., Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). *Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease*. *J Pediatr Hematol Oncol* (Vol. 37). Retrieved from www.jpho-online.com

Jamison, R. N., Serraillier, J., & Michna, E. (2011). Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain Research and Treatment*, *2011*, 941808. https://doi.org/10.1155/2011/941808

Janda, A. M., As-Sanie, S., Rajala, B., Tsodikov, A., Moser, S. E., Clauw, D. J., & Brummett, C. M. (2015). Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology*, *122*(5), 1103–1111. https://doi.org/10.1097/ALN.0000000000000637 [doi]

Knoerl, R., Lavoie Smith, E. M., & Weisberg, J. (2015). Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. *Western Journal of Nursing Research*, (Journal Article). https://doi.org/0193945915615869 [pii]

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *Journal of Pain*, *10*(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012

Lemanek, K. L., Ranalli, M., & Lukens, C. (2009). A randomized controlled trial of massage therapy in children with sickle cell disease. *Journal of Pediatric Psychology*, *34*(10), 1091–1096. https://doi.org/10.1093/jpepsy/jsp015

Leppanen, J. M. (2006). Emotional information processing in mood disorders: a review of

behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*(1), 34–39. https://doi.org/10.1097/01.yco.0000191500.46411.00

Marchand, S. (2008). The Physiology of Pain Mechanisms: From the Periphery to the Brain. *Rheumatic Disease Clinics of North America*, *34*(2), 285–309. https://doi.org/10.1016/j.rdc.2008.04.003

Martel, M O, Wasan, A. D., Jamison, R. N., & Edwards, R. R. (2013). Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. *Drug and Alcohol Dependence*, *132*(1–2), 335–341. https://doi.org/10.1016/j.drugalcdep.2013.02.034

Martel, Marc O, Jamison, R. N., Wasan, A. D., & Edwards, R. R. (2014). The association between catastrophizing and craving in patients with chronic pain prescribed opioid therapy: a preliminary analysis. *Pain Medicine (Malden, Mass.)*, *15*(10), 1757–1764. https://doi.org/10.1111/pme.12416

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Morasco, B. J., Turk, D. C., Donovan, D. M., & Dobscha, S. K. (2013). Risk for prescription opioid misuse among patients with a history of substance use disorder. *Drug and Alcohol Dependence*, *127*(1–3), 193–199. https://doi.org/10.1016/j.drugalcdep.2012.06.032

Neville, S. J., Clauw, A. D., Moser, S. E., Urquhart, A. G., Clauw, D. J., Brummett, C. M., & Harte, S. E. (2018). Association between the 2011 Fibromyalgia Survey Criteria and Multisite Pain Sensitivity in Knee Osteoarthritis. *Clinical Journal of Pain*, *34*(10), 909–917. https://doi.org/10.1097/AJP.0000000000000619

Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *Journal of Behavioral Medicine*, *20*(6), 589–605.

Phillips, K, & Clauw, D. J. (2013). Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis and Rheumatism*, *65*(2), 291–302. https://doi.org/10.1002/art.37739 [doi]

Phillips, Kristine, & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states-maybe it is all in their head. *Best Pract Res Clin Rheumatol*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005

Platt, O. S., Thorington, B. D., Brambilla, D. J., Milner, P. F., Rosse, W. F., Vichinsky, E., & Kinney, T. R. (1991). Pain in sickle cell disease. Rates and risk factors. *The New England Journal of Medicine*, *325*(1), 11–16. https://doi.org/10.1056/NEJM199107043250103 [doi]

PROMIS Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS) (Version 1.1.v 9). (n.d.). Retrieved from http://www.nihpromis.org

Quartana, P. J., Campbell, C. M., & Edwards, R. R. (2009). Pain catastrophizing: a critical review. *Expert Review of Neurotherapeutics*, *9*(5), 745–758.

https://doi.org/10.1586/ern.09.34

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F., & Treede, R. D. (2006). Quantitative sensory testing: A comprehensive protocol for clinical trials. *European Journal of Pain*, *10*(1), 77–88. https://doi.org/10.1016/j.ejpain.2005.02.003

Schatz, J., Schlenz, A. M., McClellan, C. B., Puffer, E. S., Hardy, S., Pfeiffer, M., & Roberts, C. W. (2015). Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *The Clinical Journal of Pain*, *31*(6), 536–547. https://doi.org/10.1097/AJP.0000000000000183 [doi]

Seminowicz, D. A., Shpaner, M., Keaser, M. L., Krauthamer, G. M., Mantegna, J., Dumas, J. A., … Naylor, M. R. (2013). Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *The Journal of Pain : Official Journal of the American Pain Society*, *14*(12), 1573–1584. https://doi.org/10.1016/j.jpain.2013.07.020

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., Mcclish, D. K., & Roberts, J. D. (2008). Daily Assessment of Pain in Adults with Sickle Cell Disease. *Annals of Internal Medicine*, *148*, 94–101. https://doi.org/10.7326/0003-4819-148-2-200801150-00004

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7*(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Thomas, L. S., Stephenson, N., Swanson, M., Jesse, D. E., & Brown, S. (2013). A pilot study: the effect of healing touch on anxiety, stress, pain, pain medication usage, and physiological measures in hospitalized sickle cell disease adults experiencing a vaso-occlusive pain episode. *Journal of Holistic Nursing*, *31*(4), 234–247. https://doi.org/10.1177/0898010113491631

Vacca Jr, V. M., & Blank, L. (2017). Sickle cell disease: Where are we now? *Nursing*, *47*(4), 26–34. https://doi.org/10.1097/01.NURSE.0000513609.79270.74 [doi]

Wasserman, R. A., Brummett, C. M., Goesling, J., Tsodikov, A., & Hassett, A. L. (2014). Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Regional Anesthesia and Pain Medicine*, *39*(1), 13–17. https://doi.org/10.1097/AAP.0000000000000024 [doi]

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., … Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism*, *46*(3), 319–329. https://doi.org/10.1016/j.semarthrit.2016.08.012

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(SUPPL.3). https://doi.org/10.1016/j.pain.2010.09.030

CHAPTER V

Physiologic and Psychologic Predictors of Opioid Consumption and Pain Interference

Abstract

Introduction: Many patients with sickle cell disease (SCD) experience daily pain that interferes with physical, emotional, and social functioning. Despite the prevalence of pain among these patients, few pharmacologic and non-pharmacologic management approaches effectively reduce daily pain and improve functioning. A co-occurring centrally-mediated symptom cluster, S.P.A.C.E. (i.e., sleep impairment, widespread pain, affective perturbation [depression and anxiety], cognitive impairment, and energy deficit [fatigue]) has been associated with increased daily pain among other non-SCD pain populations (e.g., fibromyalgia, temporomandibular disorder). No research has evaluated the impact of S.P.A.C.E. on opioid consumption and pain among patients with SCD.

Purpose: The purpose of this prospective, predictive study was to evaluate the predictive relationships among demographic characteristics, baseline S.P.A.C.E. symptoms, and two primary outcome variables—opioid consumption and pain interference one month post-baseline.

Patients and Methods: Baseline S.P.A.C.E. measures were completed by 48 adolescents and young adults with SCD. After baseline, participants completed weekly pain interference and opioid consumption surveys via SMS text messaging. Multi-predictor two-part models were used

to evaluate the relationships among demographic characteristics, S.P.A.C.E. symptoms, opioid consumption, and pain interference.

Results: The sample included 48 adolescents and young adults aged 14-35 ($\bar{X}$=22.8; *SD*=5.9) with SCD. All participants completed baseline measures of S.P.A.C.E. symptoms; however, only 33 completed opioid consumption and pain interference surveys post-baseline. Widespread pain significantly increased the odds of consuming opioids (*OR*=1.38). Contrary to our hypothesis, depression significantly decreased the odds of consuming opioids (*OR*=0.9). Widespread pain was the only S.P.A.C.E symptom that had a statistically significant effect on opioid consumption (β=0.16) in the subset of patients who used opioids; as widespread pain scores increased, daily opioid consumption increased by 4.62 morphine milliequivalents (MME). Within the pain interference model, female gender (*OR*=6.94) and widespread pain (*OR*=1.41) increased the odds of having pain interference. Fatigue, however, was the only S.P.A.C.E. symptom that significantly predicted pain interference (β=0.04) in the subset of patients who had pain interference scores > 0; as fatigue severity increased, total pain interference scores increased by 0.46 points.

Conclusion: Widespread pain, a common manifestation of centralized pain, was significantly predictive of opioid use. Contrary to our hypothesis, many additional S.P.A.C.E. symptoms were not significantly predictive of opioid consumption and pain interference. The lack of significant associations may be explained by the small sample size and suboptimal data completion rates. Further research should investigate the impact of S.P.A.C.E. symptoms on opioid consumption and pain in larger, more diverse sickle cell populations to guide individualized pain management. As in non-SCD pain populations, a focus on treating co-occurring symptoms with targeted

pharmacologic and non-pharmacologic approaches may be more effective in managing centralized pain than opioid therapy.

Introduction

Sickle cell disease (SCD), a commonly inherited red blood cell disease in the United States, causes several complications leading to frequent health service utilization, opioid use, and functional impairment (Ballas et al., 2017; Brown, Weisberg, Balf-Soran, & Sledge, 2015; Hildenbrand et al., 2014; Soumitri Sil et al., 2016; W T Zempsky et al., 2013). Many patients with SCD are receiving a stable dose of opioids (Patrick H Finan et al., 2018). Despite using opioids, approximately 50% of patients still report significant pain, and nearly one third continue to report pain almost every day (W R Smith et al., 2008).

Arising from research conducted with several chronic pain populations, empirical evidence suggests that pain co-occurs with several other symptoms: sleep impairment, widespread pain, affective perturbation (anxiety and depression), cognitive impairment, and low energy (fatigue), also known as the S.P.A.C.E. symptom cluster (Davis et al., 2017; Robert Knoerl et al., 2018; Shattuck & Muehlenbein, 2016; D. A. Williams, 2018). Attention to the number of symptoms experienced at one time is important because co-occurrence of multiple symptoms is associated with increased symptom burden and functional impairment (Davis et al., 2017; Robert Knoerl et al., 2018; Shattuck & Muehlenbein, 2016; D. A. Williams, 2018). Similarly, patients with SCD also experience symptoms within the S.P.A.C.E. symptom cluster (Ameringer et al., 2014; C. P. Carroll et al., 2016a; Graves & Jacob, 2014; Hoff et al., 2006; Jerrell et al., 2011; Karafin et al., 2018; Moscou-Jackson et al., 2015; S Sil, Cohen, et al., 2016; Wallen et al., 2014). More specifically, SCD patients with fatigue, depression, anxiety, and poorer sleep continuity report increased pain severity (Ameringer et al., 2014; C. P. Carroll et al.,

2016b; James L. Levenson et al., 2008; Moscou-Jackson et al., 2015). Further, evidence supports positive relationships among anxiety, depression and opioid consumption (C. P. Carroll et al., 2016b; James L. Levenson et al., 2008).

Although preliminary evidence supports the relationships among some centrally-mediated symptoms, pain, and opioid consumption, most of the research conducted among patients with SCD has only evaluated one or two S.P.A.C.E. symptoms. Empirical evidence suggests that more than 50% of patients with chronic pain present with three or more centrally-mediated symptoms (Davis et al., 2017). Given that opioids are marginally effective in treating SCD-associated pain, new, individualized pain management strategies are needed that will address interrelated symptoms that can make pain worse. Therefore, a comprehensive evaluation of the predictive relationships among all S.P.A.C.E. symptoms, pain, and opioid consumption is necessary. Using a prospective, predictive study design, the study aim was to evaluate the predictive relationships among baseline S.P.A.C.E. symptoms, average daily opioid consumption, and weekly pain interference within one month of baseline phenotyping. Based on empirical evidence, the overarching hypothesis was that baseline S.P.A.C.E. symptom severity will predict average daily opioid consumption (MME) and weekly pain interference one month post-baseline in adolescents and young adults with SCD.

Methods

Sample and Setting

Adolescents and adults with SCD (*N*=48) were recruited between 8/2019-12/2020 from the Pediatric and Adult Comprehensive Sickle Cell Clinics at Mott Children's Hospital and Michigan Medicine. Patients were included in the study if they were between the ages of 14 and 35 and could speak and read English. Patients were excluded from the study if they did not own

a smartphone. The study was approved by the University of Michigan Institutional Review Board.

Recruitment and Data Collection

Recruitment and baseline data collection procedures were previously described in Chapter III. Briefly, potentially eligible patients were pre-screened via chart review and discussion with clinic providers. The PI or trained research assistant discussed study procedures, obtained informed consent, and collected baseline data from all study participants during their outpatient clinic appointment. Two participants did not have upcoming outpatient clinic visits and completed all baseline procedures outside of the clinic.

To address the study aim, participants completed electronic Qualtrics™ surveys quantifying demographic characteristics, sleep impairment, widespread pain, anxiety, depression, cognitive function, fatigue, opioid consumption, and pain interference. The order in which participants completed the surveys was randomized via the randomizer element within Qualtrics™. Following survey completion, the PI or research assistant instructed participants on how to download the GeoPain @ Home mobile application (app) on their personal cell phone.

After baseline, participants were instructed to complete the body map in the GeoPain @ Home app every day for 30 days. Daily reminders were enabled within the app so that participants were reminded to complete body maps. To collect longitudinal pain interference and opioid consumption information, participants received a Qualtrics™ SMS text message containing a link to the pain interference and opioid consumption surveys every Friday for 30 days (four times total).

Measures

Baseline Survey. Participants self-reported their age, gender, education level, and sickle cell genotype. Sickle cell genotype was confirmed in the EMR by the PI or research assistant.

PROMIS® Short Form v1.0-Sleep-Related Impairment 8a. The 8-item PROMIS® Short Form Sleep-Related Impairment uses a 5-point Likert scale to evaluate perceptions of alertness, sleepiness, and tiredness during usual waking hours (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores meaning greater levels of sleep-related impairment. Psychometric evaluation of the measure's internal consistency reliability (α=0.92), concurrent validity, and sensitivity has been conducted in a variety of populations (i.e., healthy adolescents, females with centralized pain, and adults with SCD) (Bernstein et al., 1994; Spinhoven et al., 2014).

ACR 2011 Fibromyalgia Survey Criteria. The 19-item Widespread Pain Index (WPI) subscale, included within the ACR 2011 Fibromyalgia Survey Criteria, evaluates the presence or absence of pain over the last 7 days in 19 different body regions. Scores from the WPI range from 0 to 19 and were used to operationalize widespread pain in this study. Psychometric evaluation of the measure's internal consistency reliability (α=0.71), sensitivity, specificity, responsiveness, and validity (content and convergent) has been conducted among non-SCD pain populations (Wolfe et al., 2016).

PROMIS® Short Form v1.0 – Depression 8b. Participants reported negative mood, anhedonia, negative views of the self, and negative social cognition within the previous 7 days using the 8-item Likert-style PROMIS® Depression Short Form. (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of depression. Psychometric evaluation of the PROMIS® Depression Short Form has demonstrated the measure's internal consistency

reliability (α= 0.93), convergent validity, and sensitivity in adults with centralized pain and SCD (Keller et al., 2017; Kroenke et al., 2014).

PROMIS® Short Form v1.0 Anxiety 8a. Participants reported their fear, anxious misery, and hyper-arousal within the previous 7 days using the 8-item Likert-style PROMIS® Anxiety Short Form scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of anxiety. Psychometric evaluation of the PROMIS® Anxiety Short Form has demonstrated the measure's internal consistency reliability (α= 0.85), convergent and discriminant validity, and unidimensionality among adults with centralized pain (Irwin et al., 2010; Merriwether et al., 2017)

Multidimensional Inventory of Subjective Cognitive Impairment (MISCI). Perceived cognitive abilities and difficulties (i.e., mental clarity, memory, attention, executive functioning, and language) were quantified within the 10-item Likert-style MISCI survey (Kratz et al., 2015). Raw scores range from 10 to 50 with higher scores indicating better perceived cognitive functioning or lower cognitive impairment (Kratz et al., 2015). Psychometric evaluation of the MISCI's internal consistency reliability (α=0.94), and construct and convergent validity has been conducted among adults with centralized pain (Kratz et al., 2015).

PROMIS® Short Form v1.0-Fatigue 8a. Participants reported the impact and experience of fatigue in the past week using the 8-item Likert-style PROMIS® Fatigue Short Form (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating greater levels of fatigue. Psychometric evaluation of the PROMIS® Fatigue Short Form has demonstrated the measure's internal consistency reliability (α=0.83), test-retest reliability (ICC=0.85), concurrent and divergent validity, and sensitivity in adolescents and adults with SCD (Amtmann et al., 2010; Broderick et al., 2013; Keller et al., 2017).

PROMIS® Short Form v1.0 – Pain Interference 4a. The 8-item PROMIS® Pain Interference Short Form evaluates self-reported consequences of pain on social, cognitive, emotional, physical, and recreational activities within the previous 7 days using a 5-point Likert scale (Cella et al., 2010). Raw scores range from 8 to 40 with higher scores indicating more activity interference due to pain (Cella et al., 2010). Psychometric evaluation of the PROMIS® Pain Interference Short Form has demonstrated the measure's internal consistency reliability (α= 0.90 to 0.99), test-retest reliability (ICC 0.83 to 0.95), and sensitivity testing has been conducted in adolescents and adults with centralized pain (Amtmann et al., 2010; Broderick et al., 2013).

Opioid Consumption. Participants self-reported which, if any, opioids they were taking, and the average number of pills taken per day within the previous seven days within the Qualtrics™ Opioid Consumption survey. The average number of pills taken per day were converted into average daily milligram morphine equivalents (MME) using the Oregon Pain Guidance Opioid Conversion Calculator (2017). Participants completed the Opioid Consumption survey at baseline and every Friday for 30 days (four times total).

GeoPain @ Home Mobile Application. Participants used the interactive body map within GeoPain™ @ Home app (MoxyTech Inc., MI) to report daily pain intensity. Psychometric evaluation of the app's convergent validity and sensitivity has supported its use among patients with centralized pain (DaSilva et al., 2014; Donnell et al., 2015; DosSantos et al., 2012; Nascimento et al., 2014). Pain intensity is assessed via a color scale from 0 to 10 (using a slider bar). After selecting the intensity of their pain, participants were asked to shade the area of the body that corresponded to the chosen intensity. Prior to conducting analyses, average weekly pain intensity was calculated for each participant by taking the average of the pain scores during

each week throughout the 4-week long study period. Each participant had one baseline pain intensity score and four average weekly pain intensity scores.

Statistical Analyses

Electronic survey and mobile application data were exported from Qualtrics™ and the GeoPain @ Home internet server and analyzed using Stata software (StataCorp, 2017). Descriptive statistics (e.g. means, frequencies, 95% confidence intervals, and standard deviations) were calculated for all variables including demographic characteristics, S.P.A.C.E. symptoms, opioid consumption MME, and pain interference. Raw total scores of all PROMIS® scores were converted to T-scores (mean=50, standard deviation=10) using the PROMIS® Health Measures Scoring Service ("PROMIS® Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS®) (Version 1.1.v 9)"). PROMIS® equivalent T-scores were also used to convert cognitive function raw scores based on previously published conversion values (Kratz et al., 2015).

The Oregon Pain Guidance Opioid Conversion Calculator (2017) was used to convert opioid use to morphine milliequivalents based on the self-reported Opioid Consumption Survey and corresponding electronic medical record (EMR) dosages. One opioid consumption diary was excluded from analyses based on suspected entry error (700 MME). Six participants reported taking opioids that were discontinued. In these instances, average daily opioid consumption MME was calculated using dosages from the discontinued prescription. Further, a few participants (*n*=3) reported taking codeine with no EMR prescription history. To calculate average daily MME for these opioid consumption diaries we utilized standard-adult dosages of codeine/acetaminophen (30/300mg) from Chronic Pain Clinical Practice Guidelines (Michigan Medicine Clinical Care Guidelines, 2016).

We used multi-predictor two-part models to evaluate the predictive relationship among age, sex, S.P.A.C.E. symptoms, and the two outcome variables: pain interference and opioid consumption. Each model incorporated the nesting of observations within person (cluster-adjusted standard errors) due to the study's longitudinal design. Two-part models simultaneously use a logit model to predict the probability of a binary zero versus a positive outcome and an ordinary least squares regression model to predict the positive outcome (Belotti et al., 2015). To represent a score of zero, or having no pain interference, raw pain interference scores were rescaled to a range of 0-32 for the predictive models. The distribution of each outcome variable, with and without positive values, was evaluated prior to analyses. Each outcome variable was right skewed, even when only analyzing positive values. For this reason, we evaluated the log of each outcome variable to predict the positive values in the two-part model. To produce interpretable fitted values of the two-part models, we used a nonparametric smearing retransformation method, Duan's smearing retransformation (Duan, 1983). Consistent with Duan (1983), bootstrapping was used to re-estimate the model and re-compute unbiased standard errors and confidence intervals (Belotti et al., 2015).

Demographic covariates included within the two-part models were age and sex. Further, to account for the effect of pain intensity on pain interference and opioid consumption, we included longitudinal pain intensity scores as a covariate within each model. Thirty-four participants completed a total of 746 pain intensity scores via the GeoPain @ Home body map throughout the 30-day study period. After averaging participants' pain intensity scores each week throughout the 4-week study period, there was a total of 162 pain intensity scores that were included in the predictive analyses.

Results

Demographics

Sample demographic information of all participants (*N*=48) is provided in Table 1. Briefly, participants had a mean age of 22.8 years (range: 14-35 years). The majority of the sample were female (56.4%), African American (97.9%), and non-Hispanic (97.9%). Most of the participants had HbSS (72.9%) or HbSC (20.8%).

Data Completion

All study participants (*N*=48) completed baseline demographics, S.P.A.C.E. symptom opioid consumption, and pain interference surveys. After baseline, thirty-three participants completed 91 pain interference and 91 opioid consumption surveys (47.4% adherence).

Baseline Descriptive Statistics

S.P.A.C.E variable means, standard deviations, and score ranges are provided in Table 2. Briefly, mean scores for sleep impairment ($\bar{X}$=56.63; *SD*=9.05), cognitive function ($\bar{X}$=50.33; *SD*=4.63), and fatigue ($\bar{X}$=52.99; *SD*=11.24) were higher than PROMIS® (or equivalent) normative sample means. Mean scores for depression ($\bar{X}$=47.17; *SD*=9.53) and anxiety ($\bar{X}$=49.88; *SD*=11.42) were slightly lower than PROMIS® normative sample means. Widespread pain, or the number of body sites with pain, ranged from 0-12, with 4.02 body sites with pain reported, on average. Average daily opioid consumption varied widely at baseline among patients with a range of 0-246 MME per day ($\bar{X}$=21.83; *SD*=42.61). Lastly, baseline pain interference scores were more than 0.5 standard deviations higher than PROMIS® normative sample means ($\bar{X}$=55.56; *SD*=10.91), with a range from 41.6-75.6.

Longitudinal Descriptive Statistics

After baseline, patients reported consuming 18.58 MME of opioids per day, on average (*SD*=5.37; range=0-150). Mean pain interference scores were about 0.5 standard deviations higher than the PROMIS® normative sample mean throughout the 30-day study period ($\bar{X}$=54.45; *SD*=1.28; range=40.7-77).

Opioid Consumption Model Results

Results of the two-part model which evaluated the predictive relationships among demographics, S.P.A.C.E. symptoms, and opioid consumption are displayed in Table 1. Further, Figure 7 depicts the odds ratios and confidence intervals of the logit model. Age and female gender were not significantly associated with opioid consumption. Among the S.P.A.C.E. symptoms, widespread pain significantly increased the odds of consuming opioids [Odds Ratio (*OR)*=1.38; 95% Confidence Interval (*CI*) = 1.11 – 1.72]. Since higher scores on the Multidimensional Inventory of Subjective Cognitive Impairment are indicative of better perceived cognitive function, better perceived cognitive function significantly increased the odds of consuming opioids (*OR*=1.17*; CI* = 1.01 – 1.36). Contrary to our hypothesis, increased depression severity significantly decreased the odds of consuming opioids (*OR*=0.9; *CI*= 0.82 – 1). In the subset of patients who took opioids (*n*=30), increased symptom severity of widespread pain (β=0.16; *CI* = 0.06 – 0.26) was significantly predictive of increased opioid consumption. Contrary to our hypothesis, sleep impairment, anxiety, and fatigue were not significantly associated with opioid consumption.

The average marginal effects of S.P.A.C.E. symptoms on average daily opioid consumption MME are provided in Table 2. The average marginal effect of widespread pain was the only S.P.A.C.E. symptom significant at the 5% level. Widespread pain had a marginal effect

of 4.59 on average daily MME. Thus, as widespread pain scores increased, average daily opioid consumption increased by 4.59 MME (Figure 8).

Pain Interference Model Results

Table 3 presents the results of the two-part model which evaluated the predictive relationships among demographics, S.P.A.C.E. symptoms and pain interference. Figure 9 depicts the odds ratios and confidence intervals of the logit model. The odds of having pain interference were significantly higher in females compared to males (*OR*=6.94; *CI* = 1.02 – 47.25). Further, increased widespread pain (*OR*=1.41*; CI* = 1.13 – 1.77) increased the odds of having pain interference. In the subset of patients who had pain interference scores > 0 (*n*=40), increased fatigue (β=0.04) significantly predicted increased pain interference. Contrary to our hypothesis, sleep impairment, anxiety, depression, and cognitive function were not significantly associated with pain interference.

Table 4 provides the average marginal effects of S.P.A.C.E. symptoms on pain interference. The average marginal effect of fatigue was the only S.P.A.C.E. symptom significant at the 5% level. Fatigue had a marginal effect of 0.46 on pain interference. As fatigue scores increased, total pain interference scores increased by 0.46 points (Figure 10).

Discussion

Currently, no studies have evaluated the predictive relationships among S.P.A.C.E. symptoms, opioid consumption, and pain interference. To address this gap, we utilized a prospective, predictive study design to evaluate the relationships among demographics and baseline S.P.A.C.E. symptoms on average daily opioid consumption and weekly pain

interference for one month post-baseline. We hypothesized that increased severity of S.P.A.C.E. symptoms would predict increased opioid consumption and pain interference.

Within the opioid consumption model, widespread pain was the only S.P.A.C.E. symptom that had a positive and statistically significant relationship with opioid consumption. Its average marginal effect on opioid consumption suggests that as widespread pain increases, average daily opioid consumption increases by 4.59 MME. Within the pain interference model, greater fatigue severity was the only S.P.A.C.E. symptom significantly predictive of increased pain interference. There is a paucity of literature that has evaluated the severity and impact of fatigue on pain among patients with SCD. To our knowledge, only one study supports a significant and positive association between fatigue and pain interference (Ameringer et al., 2014).

Our findings in both the opioid consumption and pain interference models did not fully support our hypothesis. First, our study found a negative relationship among depression and opioid consumption. The ***negative*** directions of the relationships have not been previously reported from prior studies of SCD and non-SCD pain populations (Brummett et al., 2013; C. P. Carroll et al., 2016b; Grattan et al., 2012; Janda et al., 2015; J L Levenson et al., 2008). Given the ***negative*** directions of this relationships, it is important to consider potential threats to internal validity that may have biased the results. The negative relationship between depression and opioid consumption may be explained by low depression severity in our sample. More than half of our sample (62.5%) had depression severity lower than PROMIS® normative sample means. Low depression severity may have limited the ability of our predictive models to accurately detect the relationship between depression and opioid consumption.

Contrary to our hypothesis, several S.P.A.C.E. symptoms (e.g., sleep impairment, anxiety, fatigue, and cognitive function) did not significantly predict opioid consumption or pain interference. These findings conflict with research suggesting predictive relationships among depression, pain, and opioid consumption in those with SCD (C. P. Carroll et al., 2016b; James L. Levenson et al., 2008). The lack of a significant predictive relationship among many of these S.P.A.C.E. symptoms and our outcomes may be explained by statistical conclusion validity threats and uncaptured day-to-day symptom severity changes. First, our small sample size may have increased the probability of a Type II error. Second, day-to-day changes in sleep impairment, anxiety, and cognitive function severity may have threatened the internal validity of our study. Baseline assessments of these symptoms may not have accurately captured the variability in symptom severity (e.g., sleep impairment, anxiety, and fatigue) throughout the 30-day study period. Repeated measurements of S.P.A.C.E. symptoms throughout the study period may have more accurately captured daily variations in symptom severity.

As described, widespread pain was the only S.P.A.C.E. symptom to significantly predict average daily opioid consumption. Widespread pain is a common manifestation among patients with centralized pain—pain arising from altered nociception with little or no tissue damage and no evidence of disease or lesion to the somatosensory system (Lai et al., 2017; Latremoliere & Woolf, 2009; Marchand, 2008; Slade et al., 2013; Woolf, 2011). Empirical evidence suggests that patients with centralized pain disorders (i.e., fibromyalgia, temporomandibular disorder, urologic chronic pelvic pain syndrome) present with pain in multiple different body regions (Lai et al., 2017; Slade et al., 2013). Patients with centralized pain are also at risk for increased opioid consumption due to opioid non-responsiveness, or a lack of pain relief following opioid use

(Brummett et al., 2013; Corli et al., 2017; Hanks & Forbes, 1997; Janda et al., 2015; Wasserman et al., 2014).

Preliminary evidence suggests that a subset of patients with SCD (20-25%) have centralized pain (C. M. Campbell et al., 2016; C. P. Carroll et al., 2016b; E Jacob et al., 2015), and the results of the current study further validate this premise (i.e., widespread pain predictive of opioid consumption [β=0.16] and pain interference [β=0.04]). However, centralized pain is not routinely assessed within SCD clinical settings. A body map is a clinically feasible approach to evaluate widespread pain, a common centralized pain manifestation. Body maps are also easy to administer and interpret during routine outpatient visits. Clinicians can use body maps to guide clinical decisions and referrals to providers that specialized in centralized pain management (e.g., integrative health, palliative care).

Although there are validated measures that can be used to quantify the presence of centralized pain in patients with SCD, management of centralized pain, once it has been identified, remains a challenge. Non-opioid and non-pharmacologic treatments are two approaches that may be effective in managing centralized pain among patients with SCD. Non-opioid pharmacologic approaches such as antidepressants have been effective in managing pain and co-occurring symptoms (e.g., sleep) in chronic and/or centralized pain populations (Arnold, Keck, & Welge, 2000; O'Malley et al., 2000; Verdu, Decosterd, Buclin, Stiefel, & Berney, 2008). For example, evidence suggests that duloxetine, a serotonin and norepinephrine reuptake inhibitor, is effective in reducing pain among patients with chronic low back pain, chemotherapy-induced peripheral neuropathy, and fibromyalgia (Arnold et al., 2004, 2005; Skljarevski et al., 2010; Smith et al., 2013). However, no randomized control trials (RCTs) have evaluated the effectiveness of antidepressants on pain reduction among patients with SCD.

Second, non-pharmacologic interventions such as yoga, exercise, and cognitive behavioral therapy (CBT) have been effective in reducing daily pain and improving physical function among patients with centralized pain (Eller-smith et al., 2018; Hassett & Williams, 2011). However, within the SCD population, only five randomized control trials (RCTs) have evaluated the effectiveness of non-pharmacologic interventions to reduce pain with minimal or no effects (L P Barakat et al., 2010; Miriam O. Ezenwa et al., 2016; Lemanek et al., 2009; Moody et al., 2017; Schatz et al., 2015; Thomas et al., 2013). Further, no RCTs have specifically targeted patients with SCD who are experiencing centralized pain. There is a clinical need for research that evaluates the efficacy of non-opioid and non-pharmacologic interventions to reduce pain among patients who have centralized pain. As in other centralized pain populations, implementation of these interventions may reduce pain-associated burden and opioid consumption among SCD patients.

This research study has several limitations. First, our study included a small sample from one academic medical center which reduces the generalizability of our findings to all patients with SCD. Second, our small sample size may have limited the power to detect significant relationships between the predictor and outcome variables. Third, baseline assessment of S.P.A.C.E. symptoms may not have accurately captured daily variations in symptom severity throughout the study period. Fourth, adherence to weekly survey completion was 47.4% and fifteen participants did not complete any surveys post-baseline. Thus, missing data may have biased and reduced the representativeness of our findings. Our study may also be limited by potential recall bias and false reporting within the opioid consumption surveys. We excluded one opioid consumption diary with self-reported opioid consumption of 700 MME based on suspected entry error. Participants also reported taking opioid prescriptions that were absent or

discontinued from the EMR. Ultimately, our opioid consumption results should be interpreted with caution due to potential limitations of recall bias and false reporting.

In conclusion, our findings suggest that widespread pain, a common manifestation of centralized pain, may increase opioid use over time. Comprehensive evaluation of widespread pain within the clinical setting may facilitate advancements in individualized clinical care including referrals to specialists (e.g., integrative health providers and palliative care specialists). As in other non-SCD centralized pain populations, enhanced assessment and monitoring of widespread pain may be used to inform targeted interventions to reduce pain and opioid use among patients with SCD.

TABLE 13

Demographic Characteristics, N=48

Variable	*N (%)*
Age	
Mean (SD)	22.8 (5.9)
Range	14-35
Sex	
Female	27 (56.4)
Male	21 (43.8)
Race	
African American	47 (97.9)
More than one race	1 (2.1)
Ethnicity	
Not Hispanic or Latino	47 (97.9)
Unknown or do not wish to report	1 (2.1)
Education	
In middle school	1 (2.1)
In high school	11 (22.9)
Did not complete high school	3 (6.3)
Completed high school	4 (8.3)
Some college or technical training	16 (33.3)
University undergraduate degree	12 (25)
University post graduate degree	1 (2.1)
Sickle Cell Genotype	
HbSS	35 (72.9)
HbSC	10 (20.8)
HbSβ0	1 (2.1)
HbSβ+	2 (4.2)

TABLE 14

Descriptive Statistics of S.P.A.C.E. Symptoms, N=48

Variable	*Mean*	*SD*	*Minimum*	*Maximum*
PROMIS® Sleep Impairment SF	56.63	9.05	30	75
Widespread Pain Index	4.02	3.55	0	12
PROMIS® Depression SF	47.17	9.53	37.1	73.5
PROMIS® Anxiety SF	49.88	11.42	37.1	80
MISCI	50.33	4.63	44	61
PROMIS® Fatigue SF	52.99	11.24	33.1	77.7

Note. SD=standard deviation; PROMIS®=Patient Reported Outcomes Measurement Information System; SF=short form; MISCI=Multidimensional Inventory of Subjective Cognitive Impairment

Table 15

Two-part model of demographics and S.P.A.C.E. symptoms on average daily opioid consumption MME

Variables	**Two-part model**	
	Logit	**OLS**
	Odds Ratio (S.E.) [a]	*Coefficients (S.E.)* [a]
Age	0.99 (0.08)	-0.02 (0.04)
Female	1.24 (0.79)	-0.5 (0.31)
Sleep Impairment	1.01 (0.06)	-0.01 (0.02)
Widespread pain	1.38* (0.15)	0.16* (0.05)
Depression	0.9* (0.04)	-0.04 (0.03)
Anxiety	1.09 (0.06)	0.04 (0.04)
Cognitive Function	1.17* (0.09)	-0.04 (0.04)
Fatigue	1.03 (0.06)	-0.006 (0.03)

Note. MME= Morphine Milliequivalents; OLS= ordinary least squares; S.E.= standard error; OLS regression model was conditional non-zero outcome; [a] Shows the cluster-robust standard errors; *p <0.05

Table 16

Average marginal effects for S.P.A.C.E. symptoms on average daily opioid consumption MME for combined two-part model

Variables	*Observed Coefficients*[a]	*Std Error*[b]	*Z Value*	*p Value*	*95% C.I.*[b]	
					Lower Limit	*Upper Limit*
Sleep Impairment	-0.29	0.39	-0.74	0.46	-1.05	0.48
Widespread Pain	4.59	1.61	2.86	<0.00	1.44	7.75
Depression	-1.27	0.81	-1.58	0.12	-2.85	0.31
Anxiety	1.22	0.76	1.6	0.11	-0.27	2.71
Cognitive Function	-0.49	0.93	-0.52	0.6	-2.31	1.33
Fatigue	-0.04	0.73	-0.06	0.95	-1.47	1.39

[a] Duan smearing retransformation was used to obtain fitted values; [b] Nonparametric bootstrapping was used to calculate standard errors and confidence intervals; Controlling for age, gender, and pain intensity

Table 17

Two-part model of demographics and S.P.A.C.E. symptoms on pain interference

Variables	**Two-part model**	
	Logit	**OLS**
	Odds Ratio *(S.E.)* [a]	*Coefficients* *(S.E.)* [a]
Age	1.12 (0.12)	-0.004 (0.02)
Female	6.94* (6.79)	-0.08 (0.24)
Sleep Impairment	1.03 (0.05)	-0.004 (0.01)
Widespread pain	1.41* (0.16)	0.04 (0.03)
Depression	1.06 (0.07)	-0.01 (0.02)
Anxiety	0.96 (0.06)	<0.000 (0.02)
Cognitive Function	0.91 (0.07)	-0.03 (0.04)
Fatigue	1.03 (0.07)	0.04* (0.02)

Note. OLS= ordinary least squares; S.E.= standard error; OLS regression model was conditional non-zero outcome; [a] Shows the cluster-robust standard errors; *p <0.05

Table 118

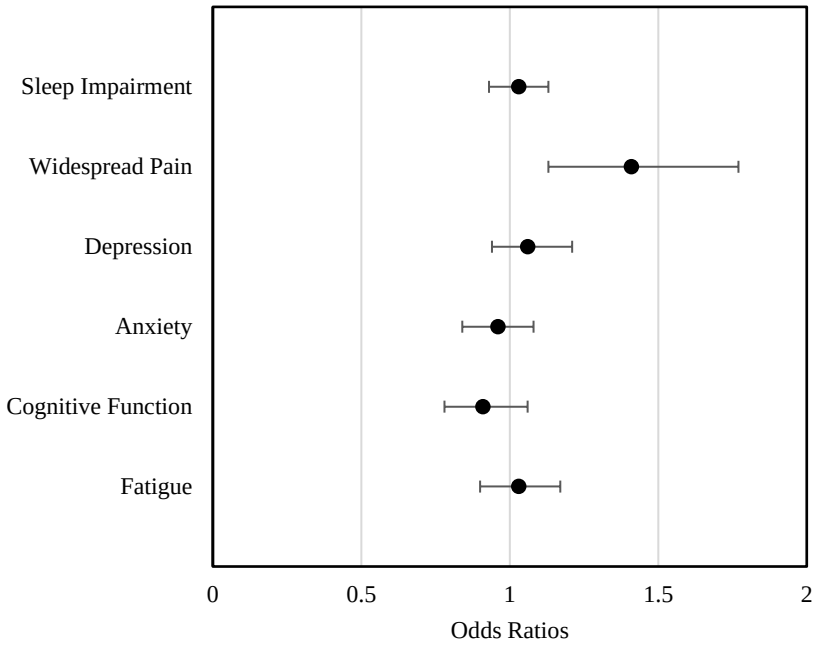
Average marginal effects for S.P.A.C.E. symptoms on pain interference for combined two-part model

Variables	*Observed Coefficients*[a]	*Std Error*[b]	*Z Value*	*p Value*	*95% C.I.*[b]	
					Lower Limit	*Upper Limit*
Sleep Impairment	-0.02	0.18	-0.11	0.91	-0.38	0.34
Widespread Pain	0.75	1.03	0.72	0.47	-1.27	2.77
Depression	-0.07	0.30	-0.23	0.82	-0.66	0.52
Anxiety	-0.04	0.21	-0.19	0.85	-0.45	0.37
Cognitive Function	-0.39	0.44	-0.89	0.37	-1.24	0.47
Fatigue	0.46	0.21	2.19	0.03	0.05	0.87

[a] Duan smearing retransformation was used to obtain fitted values; [b] Nonparametric bootstrapping was used to calculate standard errors and confidence intervals; Controlling for age, gender, and pain intensity

Figure 7

Forest plot of odds ratios and confidence intervals of S.P.A.C.E. symptoms on average daily opioid consumption MME



Note. Results from logit model; MME=morphine milliequivalents

Figure 8

Predictive margins of widespread pain on average daily opioid consumption MME

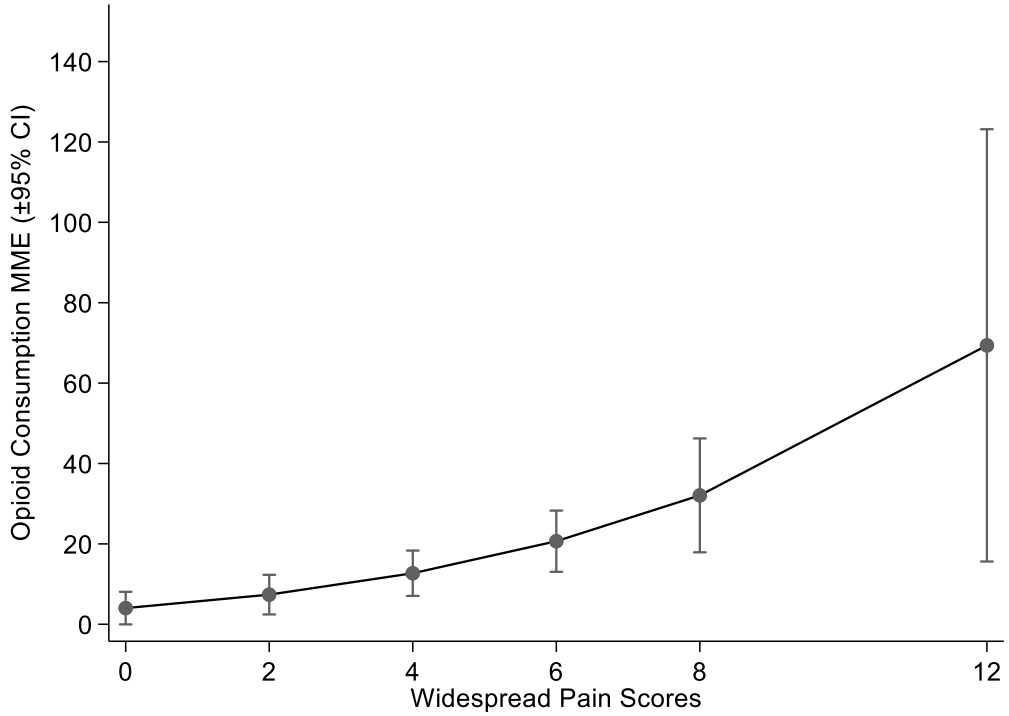
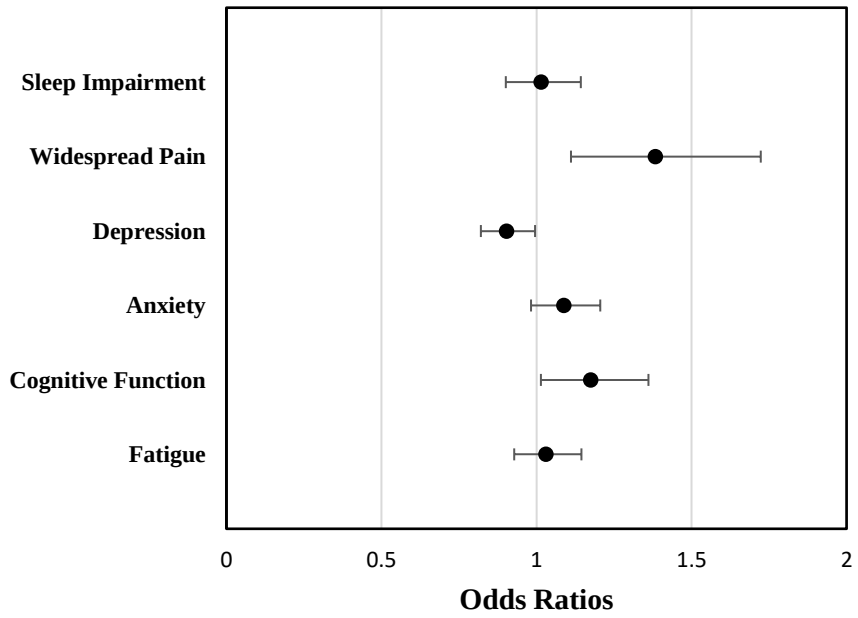


Figure 9

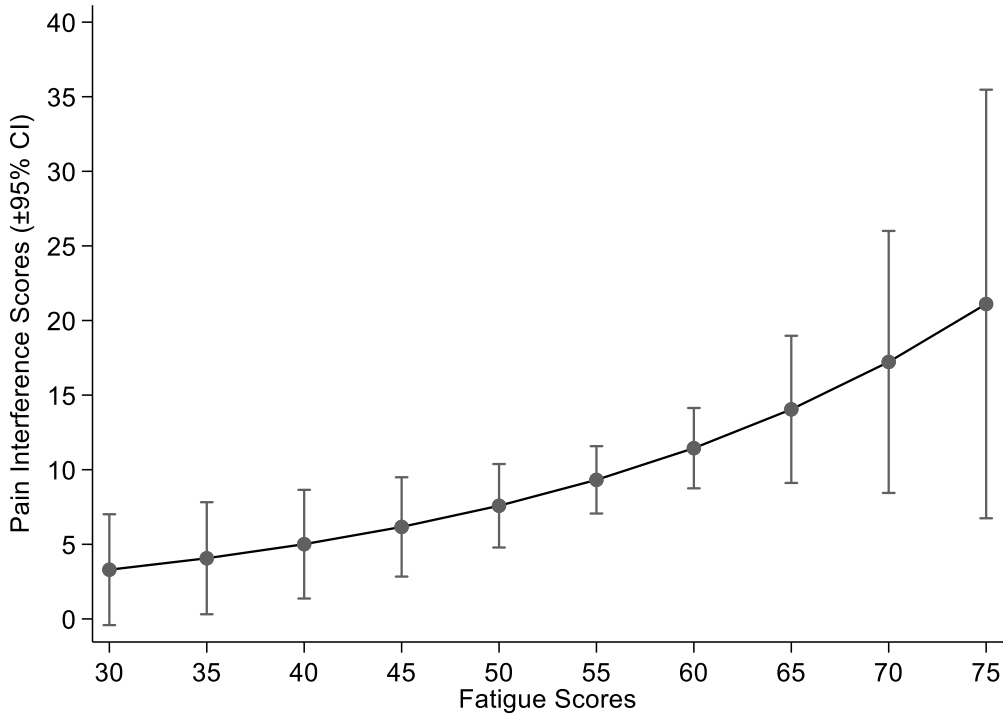
Forest plot of Odds Ratios and Confidence Intervals of S.P.A.C.E. symptoms on pain interference



Note. Results from logit model

Figure 10

Predictive margins of fatigue on pain interference



References

Arnold, L. M., Keck, P. E., & Welge, J. A. (2000). Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics*, *41*(2), 104–113. https://doi.org/10.1176/appi.psy.41.2.104

Arnold, L. M., Lu, Y., Crofford, L. J., Wohlreich, M., Detke, M. J., Iyengar, S., & Goldstein, D. J. (2004). A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis and Rheumatism*, *50*(9), 2974–2984. https://doi.org/10.1002/art.20485

Arnold, L. M., Rosen, A., Pritchett, Y. L., D'Souza, D. N., Goldstein, D. J., Iyengar, S., & Wernicke, J. F. (2005). A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*, *119*(1–3), 5–15. https://doi.org/10.1016/j.pain.2005.06.031

Ameringer, S., Elswick Jr, R. K., & Smith, W. (2014). Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing*, *31*(1), 6–17. https://doi.org/10.1177/1043454213514632 [doi]

Amtmann, D., Cook, K. F., Jensen, M. P., Chen, W. H., Choi, S., Revicki, D., … Lai, J. S. (2010). Development of a PROMIS item bank to measure pain interference. *Pain*, *150*(1), 173–182. https://doi.org/10.1016/j.pain.2010.04.025 [doi]

Bakshi, N., Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Ballas, S. K., Kanter, J., Agodoa, I., Howard, R., Wade, S., Noxon, V., & Dampier, C. (2017). Opioid Utilization Patterns in United States Patients with Sickle Cell Disease. *Blood*, *130*, 130. Retrieved from http://www.bloodjournal.org/content/130/Suppl_1/130.abstract

Barakat, L. P., Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Belotti, F., Deb, P., Manning, W. G., & Norton, E. C. (2015). twopm: Two-part models. *Stata Journal*, *15*(1), 3–20. https://doi.org/10.1177/1536867x1501500102

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132 [doi]

Broderick, J. E., Schneider, S., Junghaenel, D. U., Schwartz, J. E., & Stone, A. A. (2013). Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. *Arthritis Care & Research*, *65*(10), 1625–1633. https://doi.org/10.1002/acr.22025

Brown, S.-E., Weisberg, D. F., Balf-Soran, G., & Sledge, W. H. (2015). Sickle cell disease patients with and without extremely high hospital use: pain, opioids, and coping. *Journal of Pain & Symptom Management*, *49*(3), 539–547. https://doi.org/10.1016/j.jpainsymman.2014.06.007

Brummett, C. M., Janda, A. M., Schueller, C. M., Tsodikov, A., Morris, M., Williams, D. A., & Clauw, D. J. (2013). Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology*, *119*(6), 1434–1443. https://doi.org/10.1097/ALN.0b013e3182a8eb1f [doi]

Campbell, C. M., Moscou-Jackson, G., Carroll, C. P., Kiley, K., Haywood, C., Lanzkron, S., … Haythornthwaite, J. A. (2016). An Evaluation of Central Sensitization in Patients With Sickle Cell Disease. *The Journal of Pain*, *17*(5), 617–627. https://doi.org/10.1016/j.jpain.2016.01.475

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77. https://doi.org/10.1016/j.amepre.2016.02.012

Corli, O., Roberto, A., Bennett, M. I., Galli, F., Corsi, N., Rulli, E., & Antonione, R. (2017). Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Practice*. https://doi.org/10.1111/papr.12669 [doi]

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2017). The SPADE Symptom Cluster in Primary Care Patients with Chronic Pain. *Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286.The

Duan, N. (1983). Smearing Estimate: A Nonparametric Retransformation Method. *Journal of the American Statistical Association*, *78*(383), 605–610. https://doi.org/10.2307/2288126

Eller-smith, O. C., Nicol, A. L., Christianson, J. A., & Barr, G. A. (2018). Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions, *12*(February), 1–18. https://doi.org/10.3389/fncel.2018.00035

Ezenwa, M. O., Yao, Y., Engeland, C. G., Molokie, R. E., Wang, Z. J., Suarez, M. L., & Wilkie, D. J. (2016). A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *Journal of Advanced Nursing*, *72*(6), 1452–1463. https://doi.org/10.1111/jan.12895

Finan, P. H., Carroll, C. P., Moscou-Jackson, G., Martel, M. O., Campbell, C. M., Pressman, A., … Haythornthwaite, J. A. (2018). Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis. *The Journal of Pain*, *19*(1), 46–56. https://doi.org/10.1016/j.jpain.2017.08.010

Graves, J. K., & Jacob, E. (2014). Pain, coping, and sleep in children and adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing*, *27*(3), 109–120. https://doi.org/10.1111/jcap.12077 [doi]

Hanks, G. W., & Forbes, K. (1997). Opioid responsiveness. *Acta Anaesthesiologica Scandinavica*, *41*(1 Pt 2), 154–158.

Hassett, A. L., & Williams, D. A. (2011). Non-pharmacological treatment of chronic widespread musculoskeletal pain. *Best Practice & Research. Clinical Rheumatology*, *25*(2), 299–309. https://doi.org/10.1016/j.berh.2011.01.005

Häuser, W., Jung, E., Erbslöh-Möller, B., Gesmann, M., Kühn-Becker, H., Petermann, F., … Wolfe, F. (2012). Validation of the fibromyalgia survey questionnaire within a cross-sectional survey. *PLoS ONE*, *7*(5), 3–8. https://doi.org/10.1371/journal.pone.0037504

Hildenbrand, A. K., Nicholls, E. G., Daly, B. P., Marsac, M. L., Tarazi, R., & Deepti, R. (2014). Psychosocial and pharmacological management of pain in pediatric sickle cell disease. *Postgraduate Medicine*, *126*(2), 123–133. https://doi.org/10.3810/pgm.2014.03.2748 [doi]

Hoff, A. L., Palermo, T. M., Schluchter, M., Zebracki, K., & Drotar, D. (2006). Longitudinal relationships of depressive symptoms to pain intensity and functional disability among children with disease-related pain. *Journal of Pediatric Psychology*, *31*(10), 1046–1056. https://doi.org/jsj076 [pii]

Jacob, E., Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*, *37*(3), 185–189. https://doi.org/10.1097/MPH.0000000000000214 [doi]

Janda, A. M., As-Sanie, S., Rajala, B., Tsodikov, A., Moser, S. E., Clauw, D. J., & Brummett, C. M. (2015). Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology*, *122*(5), 1103–1111. https://doi.org/10.1097/ALN.0000000000000637 [doi]

Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary Care Companion for CNS Disorders*, *13*(2), 10.4088/PCC.10m01063. https://doi.org/10.4088/PCC.10m01063 [doi]

Karafin, M. S., Singavi, A., Hussain, J., Wandersee, N., Heinrich, T., Hurley, R. W., … Field, J. J. (2018). Predictive factors of daily opioid use and quality of life in adults with sickle cell disease. *Hematology*, *8454*(May), 1–8. https://doi.org/10.1080/10245332.2018.1479997

Keller, S., Yang, M., Treadwell, M. J., & Hassell, K. L. (2017). Sensitivity of alternative measures of functioning and wellbeing for adults with sickle cell disease: comparison of PROMIS(R) to ASCQ-Me. *Health and Quality of Life Outcomes*, *15*(1), 115–117. https://doi.org/10.1186/s12955-017-0661-5 [doi]

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2018). Estimating the Frequency , Severity , and Clustering of SPADE Symptoms in Chronic Painful Chemotherapy- Induced Peripheral Neuropathy. *Pain Management Nursing*, *19*(4), 354–365.

https://doi.org/10.1016/j.pmn.2018.01.001

Kratz, A. L., Schilling, S. G., Goesling, J., & Williams, D. A. (2015). Development and Initial Validation of a Brief Self-Report Measure of Cognitive Dysfunction in Fibromyalgia. *The Journal of Pain*, *16*(6), 527–536. https://doi.org/10.1016/j.jpain.2015.02.008

Kroenke, K., Yu, Z., Wu, J., Kean, J., & Monahan, P. O. (2014). Operating characteristics of PROMIS four-item depression and anxiety scales in primary care patients with chronic pain. *Pain Medicine (Malden, Mass.)*, *15*(11), 1892–1901. https://doi.org/10.1111/pme.12537

Lai, H. H., Jemielita, T., Sutcliffe, S., Bradley, C. S., Naliboff, B., Williams, D. A., … Landis, J. R. (2017). Characterization of Whole Body Pain in Urological Chronic Pelvic Pain Syndrome at Baseline: A MAPP Research Network Study. *The Journal of Urology*, *198*(3), 622–631. https://doi.org/10.1016/j.juro.2017.03.132

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *Journal of Pain*, *10*(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012

Lemanek, K. L., Ranalli, M., & Lukens, C. (2009). A randomized controlled trial of massage therapy in children with sickle cell disease. *Journal of Pediatric Psychology*, *34*(10), 1091–1096. https://doi.org/10.1093/jpepsy/jsp015

Levenson, J. L., McClish, D. K., Dahman, B. A., Bovbjerg, V. E., De A. Citero, V., Penberthy, L. T., … Smith, W. R. (2008). Depression and anxiety in adults with sickle cell disease: The PiSCES project. *Psychosomatic Medicine*, *70*(2), 192–196. https://doi.org/10.1097/PSY.0b013e31815ff5c5

Marchand, S. (2008). The Physiology of Pain Mechanisms: From the Periphery to the Brain. *Rheumatic Disease Clinics of North America*, *34*(2), 285–309. https://doi.org/10.1016/j.rdc.2008.04.003

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Moscou-Jackson, G., Finan, P. H., Campbell, C. M., Smyth, J. M., & Haythornthwaite, J. A. (2015). The effect of sleep continuity on pain in adults with sickle cell disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010

Neville, S. J., Clauw, A. D., Moser, S. E., Urquhart, A. G., Clauw, D. J., Brummett, C. M., & Harte, S. E. (2018). Association between the 2011 Fibromyalgia Survey Criteria and Multisite Pain Sensitivity in Knee Osteoarthritis. *Clinical Journal of Pain*, *34*(10), 909–917. https://doi.org/10.1097/AJP.0000000000000619

O'Malley, P. G., Balden, E., Tomkins, G., Santoro, J., Kroenke, K., & Jackson, J. L. (2000). Treatment of fibromyalgia with antidepressants: A meta-analysis. *Journal of General Internal Medicine*, *15*(9), 659–666. https://doi.org/10.1046/j.1525-1497.2000.06279.x

PROMIS Cooperative Group. Unpublished manual for the Patient Reported Outcomes Measurement Information System (PROMIS) (Version 1.1.v 9). (n.d.). Retrieved from http://www.nihpromis.org

Schatz, J., Schlenz, A. M., McClellan, C. B., Puffer, E. S., Hardy, S., Pfeiffer, M., & Roberts, C. W. (2015). Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *The Clinical Journal of Pain*, *31*(6), 536–547. https://doi.org/10.1097/AJP.0000000000000183 [doi]

Shattuck, E. C., & Muehlenbein, M. P. (2016). Towards an integrative picture of human sickness behavior. *Brain, Behavior, and Immunity*, *57*, 255–262. https://doi.org/10.1016/j.bbi.2016.05.002

Sil, S, Cohen, L. L., & Dampier, C. (2016). Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *The Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289 [doi]

Sil, Soumitri, Cohen, L. L., & Dampier, C. (2016). Psychosocial and functional outcomes in youth with chronic sickle cell pain. *Clinical Journal of Pain*, *32*(6), 527–533. https://doi.org/10.1097/AJP.0000000000000289

Skljarevski, V., Desaiah, D., Liu-Seifert, H., Zhang, Q., Chappell, A. S., Detke, M. J., … Backonja, M. (2010). Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine*, *35*(13), E578-85. https://doi.org/10.1097/BRS.0b013e3181d3cef6

Slade, G. D., Smith, S. B., Zaykin, D. V, Tchivileva, I. E., Gibson, D. G., Yuryev, A., … Diatchenko, L. (2013). Facial pain with localized and widespread manifestations: separate pathways of vulnerability. *Pain*, *154*(11), 2335–2343. https://doi.org/10.1016/j.pain.2013.07.009

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., … Oncology, A. for C. T. in. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama*, *309*(13), 1359–1367. https://doi.org/10.1001/jama.2013.2813

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., McClish, D. K., Roberts, J. D., Dahman, B., … Roseff, S. D. (2008). Daily assessment of pain in adults with sickle cell disease. *Annals of Internal Medicine*, *148*(2), 94–101. https://doi.org/148/2/94 [pii]

Spinhoven, P., Penninx, B. W., Hickendorff, M., van Hemert, A. M., Bernstein, D. P., & Elzinga, B. M. (2014). Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. *Psychological Assessment*, *26*(3), 717–729. https://doi.org/10.1037/pas0000002

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Thomas, L. S., Stephenson, N., Swanson, M., Jesse, D. E., & Brown, S. (2013). A pilot study: the effect of healing touch on anxiety, stress, pain, pain medication usage, and physiological measures in hospitalized sickle cell disease adults experiencing a vaso-occlusive pain episode. *Journal of Holistic Nursing*, *31*(4), 234–247. https://doi.org/10.1177/0898010113491631

Verdu, B., Decosterd, I., Buclin, T., Stiefel, F., & Berney, A. (2008). Antidepressants for the treatment of chronic pain. *Drugs*, *68*(18), 2611–2632. Retrieved from https://link.springer.com/content/pdf/10.2165%2F0003495-200868180-00007.pdf

Wallen, G. R., Minniti, C. P., Krumlauf, M., Eckes, E., Allen, D., Oguhebe, A., … Taylor, J. G. (2014). Sleep disturbance, depression and pain in adults with sickle cell disease. *BMC Psychiatry*, *14*, 207. https://doi.org/10.1186/1471-244X-14-207

Wasserman, R. A., Brummett, C. M., Goesling, J., Tsodikov, A., & Hassett, A. L. (2014). Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Regional Anesthesia and Pain Medicine*, *39*(1), 13–17. https://doi.org/10.1097/AAP.0000000000000024 [doi]

Williams, D. A. (2018). Phenotypic features of central sensitization. *Journal of Applied Biobehavioral Research*, *23*(2), 1–15. https://doi.org/10.1111/jabr.12135

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., … Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism*, *46*(3), 319–329. https://doi.org/10.1016/j.semarthrit.2016.08.012

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(SUPPL.3). https://doi.org/10.1016/j.pain.2010.09.030

Zempsky, W T, Palermo, T. M., Corsi, J. M., Lewandowski, A. S., Zhou, C., & Casella, J. F. (2013). Daily changes in pain, mood and physical function in children hospitalized for sickle cell disease pain. *Pain Research & Management*, *18*(1), 33–38.

Zempsky, William T., Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread pain among youth with sickle cell disease hospitalized with vasoocclusive pain. *Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403

CHAPTER VI

Summary

Sickle cell disease (SCD) is the most commonly inherited red blood cell disorder in the United States and causes several negative sequelae including organ damage, frequent health service utilization, and pain (Platt et al., 1991; Vacca Jr & Blank, 2017). Pain, known as the hallmark complication of SCD, has been associated with reduced function, poor quality of life, anxiety, and depression (Adam et al., 2017; Benton, Ifeagwu, & Smith-Whitley, 2007; Jerrell, Tripathi, & McIntyre, 2011; Smith, Penberthy, Bovbjerg, Mcclish, & Roberts, 2008). Although pain impacts the lives of many patients with SCD, few effective pharmacologic and non-pharmacologic pain management strategies reduce pain in these patients. Pain is a complex multidimensional problem that is influenced by numerous physical (e.g., central pain mechanisms), psychological (e.g., anxiety, depression), and cognitive factors (e.g., cognitive impairmentfunction), which if addressed, might advance the science of SCD pain management. The literature is sparse regarding the influence of multidimensional factors on pain among patients with SCD. Thus, to understand the multidimensional and individualized presentation of pain among patients with SCD, we used a prospective, predictive, correlation study design to achieve the following four aims: 1) describe the incidence and severity of several pain influencing factors including pain catastrophizing, centralized pain, and S.P.A.C.E. symptoms (sleep impairment, multifocal pain, depression, anxiety, cognitive function, fatigue) in adolescents and young adults (14-35 years) with SCD; 2) evaluate the predictive relationships

among S.P.A.C.E. symptoms, opioid consumption, and pain interference; 3) examine the predictive relationships among pain catastrophizing, centralized pain, opioid consumption, and pain interference; and, 4) characterize the co-occurrence of baseline S.P.A.C.E. symptoms, pain interference, opioid consumption, pain intensity, and P.A.I.N.S. (a metric that combines pain intensity and widespread pain) among adolescents and young adults with SCD.

Results

Sample

The study sample consisted of 48 adolescents and young adults with SCD receiving care within the Michigan Medicine Pediatric and Adult Comprehensive Sickle Cell Clinics. Participants were 14-35 years old with an average age of 22.8 years (SD=5.9). The sample was mainly female, African American, college educated, and most had been diagnosed with the HbSS and HbSC genotypes. All participants completed baseline survey measures. However, three participants were unable to provide baseline pain intensity, widespread pain, and P.A.I.N.S. data from the GeoPain @ Home mobile app. After baseline, 33 participants completed 91 opioid consumption and 91 pain interference surveys throughout the 30-day study period (47.4% adherence). One baseline opioid consumption diary was excluded based on suspected entry error; the participant reported taking an extremely high opioid dose (700 morphine milliequivalents [MME]).

Specific Aim 1

The first specific aim was to characterize demographic variables (i.e., age, sex, and sickle cell genotype), the incidence and severity of centralized pain, pain catastrophizing, and six S.P.A.C.E. symptoms (i.e., sleep impairment, widespread pain, anxiety, depression, cognitive function, fatigue) measured at baseline among adolescents and adults with SCD.

Findings. Forty-eight adolescents and young adults with SCD aged 14 to 35 years completed baseline measures of centralized pain, pain catastrophizing, and S.P.A.C.E. symptoms. Mean pain catastrophizing scores were low ($\bar{X}$=16.23; *SD*=13.36) with thirty-six participants (75%) reporting total pain catastrophizing scores ≤ 25 (less catastrophic thinking about pain). One-fourth of the participants (*n*=12) had a positive centralized pain score (total score ≥ 13). Participants reported having pain within 0 to 12 body sites, with an average of 4.02 body sites reported. Sample means of three S.P.A.C.E. symptoms were higher than normative sample means (PROMIS® or equivalent) were sleep impairment ($\bar{X}$=56.63; *SD*=9.05), cognitive function ($\bar{X}$=50.33; *SD*=4.63), and fatigue ($\bar{X}$=52.99; *SD*=11.24). The remaining S.P.A.C.E. symptoms had mean scores that were similar to PROMIS® normative sample means (depression [$\bar{X}$=47.17; *SD*=9.53] and anxiety [$\bar{X}$=49.88; *SD*=11.42]).

Discussion. This study comprehensively described multidimensional physiologic and psychologic pain characteristics including pain catastrophizing, centralized pain, and S.P.A.C.E. symptoms. Sleep impairment and fatigue severity within our sample are consistent with previous SCD research (Ameringer et al., 2014; Daniel et al., 2010; Mann-Jiles et al., 2015; Moody et al., 2017; Sharma et al., 2015). Low severity of depression, anxiety, and pain catastrophizing conflicts with research conducted among patients with SCD (N Bakshi et al., 2018, 2017; Jerrell et al., 2011; Laurence et al., 2006; Ozer et al., 2014). Low severity of these pain influencing factors may be explained by the overall low pain intensity ($\bar{X}$=3.41) of our sample. Empirical evidence suggests that depression, anxiety, and pain catastrophizing are all associated with pain (C. M. Campbell, Kronfli, et al., 2011; Davis et al., 2017; Maletic & Raison, 2009; McWilliams et al., 2003, 2004; Strigo et al., 2008; Tsang et al., 2008). Thus, greater depression, anxiety, and pain catastrophizing severity may have been found if the pain intensity of our sample was higher.

The incidence of centralized pain described is consistent with SCD research that has evaluated centralized pain using quantitative sensory testing methods (C. M. Campbell et al., 2016; C. P. Carroll et al., 2016a; Eufemia Jacob et al., 2015). Further, variability in widespread pain, a common manifestation of centralized pain, is consistent with research conducted with the sickle cell population (McClish et al., 2009; Zempsky et al., 2017).

Specific Aim 2

The second specific aim was to evaluate the predictive relationships of demographic variables (i.e., age and sex) and baseline S.P.A.C.E. symptoms (sleep impairment, multifocal pain, anxiety, depression, cognitive function, fatigue) on average daily opioid consumption and weekly pain interference reported longitudinally for one month post-baseline in adolescents and young adults with SCD.

Findings. Widespread pain significantly increased the odds of consuming opioids. In the subset of patients who used opioids, widespread pain was the only S.P.A.C.E symptom that had a statistically significant effect on average daily opioid consumption. Contrary to our hypothesis, depression significantly decreased the odds of consuming opioids. Further, better perceived cognitive function was significantly increased the odds of consuming opioids. Lastly, sleep impairment, anxiety, and fatigue were not significantly associated with average daily opioid consumption. Within the pain interference model, female gender and widespread pain significantly increased the odds of having pain interference. Fatigue was the only S.P.A.C.E. symptom that significantly predicted pain interference in the subset of patients who had pain interference scores > 0. Contrary to our hypothesis, sleep impairment, anxiety, depression, and cognitive function were not significantly associated with pain interference.

Discussion. These findings suggest that widespread pain was the only S.P.A.C.E. symptom that significantly predicted opioid consumption. Patients with centralized pain conditions (e.g., temporomandibular disorder, fibromyalgia) frequently report widespread pain distributions (Cassisi et al., 2014; Lai et al., 2017; Slade et al., 2013). Further, higher centralized pain survey scores (i.e., American College of Rheumatology (ACR) 2011 Fibromyalgia Survey Criteria), which include a measure of widespread pain, have been predictive of opioid consumption in non-SCD populations (Brummett et al., 2013; Janda et al., 2015). If opioids are ineffective in reducing pain, patients commonly increase the dosage, resulting in opioid non-responsiveness (opioid consumption with little benefit). Although evidence suggests that patients with centralized pain are at an increased risk for opioid non-responsiveness (Corli et al., 2017; Hanks & Forbes, 1997; Wasserman et al., 2014), centralized pain is rarely identified and evaluated among patients with SCD. Centralized pain should be evaluated in clinical and research settings to (1) identify patients at risk for opioid non-responsiveness, (2) facilitate referrals to specialists (e.g., integrative health practitioners, palliative care providers), and (3) support the use of alternative pharmacologic, and/or non-pharmacologic pain management approaches.

Within the pain interference model, fatigue significantly predicted pain interference, or pain that interferes with social, emotional, and physical functioning. Empirical evidence supports this predictive relationship among non-SCD pain populations (Davis et al., 2017; Robert Knoerl et al., 2018). Interestingly, few research studies have evaluated the impact of fatigue on pain among patients with SCD. Only one study supports a significant positive relationship between fatigue and pain interference (Ameringer et al., 2014).

Contrary to our hypothesis, sleep impairment, anxiety, and fatigue were not significantly predictive of opioid consumption. Further, widespread pain, cognitive function, and anxiety were not significantly related to increased pain interference. The lack of significance among these S.P.A.C.E. symptoms and important clinical outcomes may be explained by our small sample size. Our sample size may have threatened the statistical conclusion validity of our findings by increasing the probability of a Type II error. Further, day-to-day variations in symptom severity may have threatened the internal validity of our study. It is possible that baseline/cross-sectional measurement did not capture the variability in symptom severity (e.g., sleep impairment, anxiety, and fatigue) throughout the one month study period. Repeated measurements of S.P.A.C.E. symptoms may have more accurately captured daily variations in symptom severity, and when averaged over time, may result in mean scores that are more reflective of everyday life with SCD. For this reason, daily evaluations of symptoms are recommended to accurately capture the day-to-day symptom experience.

Our study found a negative relationship among depression and opioid consumption. The ***negative*** directions of the relationships have not been previously reported from prior studies of SCD and non-SCD pain populations (Brummett et al., 2013; C. P. Carroll et al., 2016b; Grattan et al., 2012; Janda et al., 2015; J L Levenson et al., 2008). Given the ***negative*** directions of this relationships, it is important to consider potential threats to internal validity that may have biased the results. The negative relationship between depression and opioid consumption may be explained by a lack of variability in depression scores. Since a majority of our sample had depression severity lower than PROMIS® normative sample means, our predictive model may have been unable to accurately predict the relationship between depression and opioid consumption.

Specific Aim 3

The third specific aim was to examine the predictive relationships among baseline centralized pain and pain catastrophizing severity on average daily opioid consumption and weekly pain interference within one month of baseline phenotyping.

Findings. Centralized pain significantly increased the odds of consuming opioids and having pain interference. Further, among those who consumed opioids and had pain interference, increased centralized pain significantly predicted more opioid use and pain interference. Contrary to our hypothesis, pain catastrophizing significantly predicted less opioid consumption. In the pain interference model, higher pain catastrophizing scores significantly increased the odds of having pain interference. However, pain catastrophizing scores did not significantly predict longitudinal pain interference in the subset of patients that had pain interference scores > 0.

Discussion. Our findings and emerging evidence suggest that centralized pain occurs in a subset of patients with SCD (Brandow, Stucky, Hillery, Hoffmann, & Panepinto, 2013; Campbell et al., 2016; Carroll et al., 2016; Jacob et al., 2015). As discussed, non-pharmacologic pain management approaches are preferred to pharmacologic agents (opioids), which are often ineffective in centralized pain populations. However, little is known about the efficacy of non-pharmacological interventions among patients with SCD. Only five non-pharmacologic randomized control trials (RCTs) have been conducted in the SCD population with little or no effect on daily pain (L P Barakat et al., 2010; Miriam O. Ezenwa et al., 2016; Lemanek et al., 2009; Moody et al., 2017; Schatz et al., 2015; Thomas et al., 2013). Limited effects found in these studies may be explained by the study samples. None of the RCTs specifically targeted

patients with centralized pain. Therefore, patients without centralized pain may have confounded the treatment effect found within the entire sample.

In our study, centralized pain was significantly predictive of opioid consumption and pain that interferes with social, emotional, and physical functioning. These findings are consistent with evidence from prior studies of non-SCD centralized pain populations (Cassisi et al., 2014; Kristine Phillips & Clauw, 2011; Wasserman et al., 2014). When an opioid is ineffective in reducing pain, patients and clinicians commonly increase the dosage, which consequently results in opioid non-responsiveness; patients take greater opioid dosages but experience little benefit (Brummett et al., 2013; Hanks & Forbes, 1997; Janda et al., 2015; Wasserman et al., 2014). To reduce the use of ineffective pharmacologic agents like opioids, non-pharmacologic interventions are encouraged (Hassett & Williams, 2011; Winfried Hauser, Bernardy, Arnold, Offenbacher, & Schiltenwolf, 2009).

Although emerging evidence suggests that centralized pain impacts opioid consumption and function among patients with SCD, it is rarely evaluated and considered within clinical practice. Our study utilized a more feasible approach to evaluate centralized pain—a reliable and valid patient-reported outcome (PRO) measure. The PRO measure used within our study, the ACR 2011 Fibromyalgia Survey Criteria, may be a useful tool to identify patients experiencing centralized pain. Ultimately, centralized pain evaluation could guide clinicians in the implementation of individualized non-pharmacologic interventions, such as exercise and cognitive behavioral therapy, that have been efficacious in reducing pain and improving function in non-SCD centralized pain populations (Hassett & Williams, 2011; Robert Knoerl, Lavoie Smith, & Weisberg, 2016).

The negative relationships among increased pain catastrophizing and opioid consumption conflicts with empirical evidence in SCD and non-SCD populations. Our conflicting findings may be explained by low symptom severity and recall bias. First, there was a lack of variability in pain catastrophizing scores within our sample. Mean pain catastrophizing scores found within our study were much less than those previously reported among patients with SCD (N Bakshi et al., 2017). Low symptom severity may have limited the ability of our statistical models to accurately predict the effects of pain catastrophizing on opioid consumption and pain interference. Second, our pain catastrophizing findings may have been confounded by recall bias. Participants are asked to recall a past painful event when answering the pain catastrophizing survey questions. Since many participants in our sample reported no pain at baseline, it may have been difficult to accurately recall a past painful event when answering the questions. In summary, the negative relationships found among pain catastrophizing, opioid consumption, and pain interference should be interpreted with caution due to low symptom severity and potential recall bias.

Specific Aim 4

The fourth specific aim was to characterize the co-occurrence of baseline S.P.A.C.E. symptoms, average daily opioid consumption, pain interference, pain intensity, and Pain Area and Intensity Number Summation (P.A.I.N.S.) measured via an interactive body map within the GeoPain @ Home mobile application.

Findings. Many S.P.A.C.E. symptoms (i.e., sleep impairment, anxiety, depression, cognitive function, and fatigue) were moderately and significantly correlated with one another. Pain interference was moderately and significantly correlated with all but one S.P.A.C.E.

symptom (depression). Widespread pain was the only S.P.A.C.E. symptom that was significantly associated with average daily opioid consumption, pain intensity, and P.A.I.N.S.

Discussion. This study is the first to evaluate the co-occurrence of all symptoms within the S.P.A.C.E. symptom cluster. Consistent with research conducted in non-SCD pain populations, many S.P.A.C.E. symptoms were moderately and significantly correlated (Davis et al., 2017; Robert Knoerl et al., 2018; Shattuck & Muehlenbein, 2016). Surprisingly, widespread pain was the only S.P.A.C.E. symptom that was not correlated with any other symptoms. Limited research has investigated the relationships among S.P.A.C.E. symptoms and widespread pain in patients with SCD. Our findings suggest that widespread pain may not be a significant contributor to the S.P.A.C.E. symptom cluster. These findings may also be explained by our small sample size and low symptom severity of our sample. First, our small sample size may have increased the probability of a Type II error (false negative). Further, correcting for multiple comparisons (Bonferroni) led to a reduction in the level of significance. A reduced level of significance may have subsequently increased the probability of a Type II error. Second, low pain and symptom severity within our sample may have biased the precision of our statistical analyses. The only S.P.A.C.E. symptoms that were higher than PROMIS® (or equivalent) normative sample means were sleep impairment, cognitive function, and fatigue. Further, baseline pain severity of our sample was low ($\bar{X}$=3.41). Ultimately, our findings may have been biased due to our small sample size and low symptom severity.

Interestingly. widespread pain was the only S.P.A.C.E. symptom that significantly correlated with average daily opioid consumption, pain intensity, and P.A.I.N.S. Our study was unable to detect any statistically significant correlations between the remaining S.P.A.C.E. symptoms, opioid use, and pain. These findings conflict with empirical evidence that suggests

positive and significant relationships between S.P.A.C.E. symptoms, opioid consumption, and pain (Ameringer et al., 2014; C. P. Carroll et al., 2016a; James L. Levenson et al., 2008; Moscou-Jackson et al., 2015). As discussed previously, the lack of statistically significant associations found within our study may be explained by an increased probability of a Type II error (i.e., small sample size and correction for multiple comparisons).

Many S.P.A.C.E. symptoms were significantly associated with pain that interferes with social, cognitive, emotional, and physical functioning. These findings highlight the importance of evaluating multidimensional symptoms, like S.P.A.C.E., during routine clinical visits. Early identification of severe S.P.A.C.E. symptoms can facilitate individualized care management. Clinicians may use knowledge of S.P.A.C.E. symptom severity to guide referrals to ancillary psychiatric resources and specialists such as palliative care and integrative health providers. Ultimately, identification and management of S.P.A.C.E. symptoms may lead to reductions in daily pain and improvements in functioning and quality of life among patients with SCD.

Limitations

This dissertation study has several limitations. As described, low symptom severity of pain and S.P.A.C.E. symptoms (i.e., depression and anxiety) may have limited the precision of our statistical analyses. Further, our small sample size may have influenced the statistical significance of our findings by increasing the probability of Type II errors. Adherence to longitudinal data collection was suboptimal (47.3%) within our sample. Thus, our findings may have been biased by missing data. Another limitation of our study is evidence of false reporting and entry error within opioid consumption surveys. Many participants reported taking opioids that were discontinued in the electronic medical record (EMR). For these instances, we utilized discontinued dosages to calculate MME. Additionally, some participants (n=3) reported taking

codeine with no evidence of prescription history. Since it is plausible that these three participants received codeine prescriptions from outside institutions, we used standard-adult dosages of codeine/acetaminophen (30/300mg) from Chronic Pain Clinical Practice Guidelines to calculate their MME (Michigan Medicine Clinical Care Guidelines, 2016). Lastly, we excluded one baseline opioid consumption diary (700 MME) due to suspected entry error. Ultimately, self-reported opioid consumption may have been biased due to false reporting and entry error. Although this research evaluated a wide variety of multidimensional symptoms that may impact pain and opioid consumption, there are many other pain-related factors that were not included as variables within this study such as sickle cell genotype, pain control beliefs, stigma, social support, and trauma exposure. It is possible that these factors influence pain and opioid consumption and confounded the findings in our study. Lastly, our study was conducted within one academic medical center which limits the generalizability of our findings to all adolescents and young adults with SCD.

Recommendations for Future Research

The limitations of our research can guide the design of future SCD research studies. First, low symptom severity of our sample may have confounded the precision of our statistical analyses. Future research conducted among patients with SCD should limit inclusion to patients that are experiencing a certain level of daily pain (e.g., baseline pain intensity ≥ 4 out of 10).

Second, the current study did not evaluate the relationships among several pain-influencing factors (i.e., sickle cell genotype, pain control beliefs, stigma, social support, and trauma exposure), pain, and opioid consumption. Research conducted among SCD and non-SCD populations suggests that many of these factors may influence pain outcomes (Carter et al., 2002; Forgeron et al., 2010; W Hauser et al., 2011; Holtzman et al., 2004; Kanzawa-Lee et al., 2018;

Oram et al., 2012; K Phillips & Clauw, 2011; Schofferman et al., 1993; Snelling, 1994; Spiegel et al., 2015; Zaza & Baine, 2002). However, there is a paucity of literature that has evaluated the relationships among stigma, pain control beliefs, social support, trauma exposure, pain, and opioid consumption in the SCD population. (Bediako et al., 2016; P. C. Carroll et al., 2013; Ford et al., 2017; Martin et al., 2018). To address this gap in the literature, future SCD research should consider evaluating the relationships of these pain-influencing factors, pain, and opioid use.

Third, this dissertation study was limited by low data completion rates and potential false reporting of opioid use. To try and address low data adherence, our study set up daily reminders within the GeoPain @ Home mobile application. Low adherence to daily pain diary completion (51.8%) suggests that daily app reminders were not effective. Further, participants received a weekly text message every Friday including a reminder to complete daily pain diaries. Weekly pain interference and opioid consumption survey links were also included within the text message. Adherence to weekly survey completion was also low (47.4%). Text messages were sent every Friday throughout the 30-day study period. It is possible that sending text messages during a different day of the week (e.g., Wednesday) would increase data completion rates. Further, future longitudinal studies may implement additional strategies to increase data completion rates such as reminder calls and text messages throughout the week.

The findings of this dissertation study demonstrated the incidence of centralized pain and its influence on pain and opioid consumption among patients with SCD. Future research that specifically targets the centralized pain population is necessary to guide SCD clinical care and reduce pain and opioid consumption. Effective non-opioid and non-pharmacologic approaches used within centralized pain populations may inform future research among patients with SCD. First, evidence supports the effectiveness of non-opioid pharmacologic interventions such as

antidepressants in managing pain and co-occurring symptoms among chronic and centralized pain populations (Arnold, Keck, & Welge, 2000; O'Malley et al., 2000; Verdu, Decosterd, Buclin, Stiefel, & Berney, 2008). For example, duloxetine, a serotonin and norepinephrine reuptake inhibitor, has been effective in reducing pain among patients with fibromyalgia, chronic low back pain, and chemotherapy-induced peripheral neuropathy (Arnold et al., 2004, 2005; Skljarevski et al., 2010; Smith et al., 2013). Despite empirical evidence in non-SCD populations, no randomized control trials (RCTs) have evaluated the effectiveness of antidepressants in managing pain among patients with SCD. Second, non-pharmacologic interventions such as yoga, exercise, and cognitive behavioral therapy (CBT) are recommended for patients with centralized pain in non-SCD populations (Büssing et al., 2012; Hassett & Williams, 2011; Robert Knoerl et al., 2016). For example, CBT interventions have been effective in reducing pain and improving function among patients with fibromyalgia, chronic low back pain, and temporomandibular disorder (Hassett & Williams, 2011; Robert Knoerl et al., 2016). Interventions testing CBT use a wide variety of cognitive and behavioral strategies (e.g., hypnosis, guided imagery, coping skills training, and progressive muscle relaxation) to produce desired effects.

To our knowledge, five randomized control trials (RCTs) have tested the efficacy of non-pharmacologic interventions among patients with SCD (L P Barakat et al., 2010; Miriam O. Ezenwa et al., 2016; Lemanek et al., 2009; Moody et al., 2017; Schatz et al., 2015; Thomas et al., 2013). Only two of these RCTs have tested CBT-based intervention strategies with minimal or no effects in pain reduction (Lamia P. Barakat et al., 2010; Schatz et al., 2015). However, these studies were limited by internal validity threats including small sample sizes, no participant blinding, and a lack of intervention standardization, which may explain the lack of efficacy.

Based on our findings and the established evidence supporting the use of CBT among centralized pain populations (Hassett & Williams, 2011; R Knoerl et al., 2015), future non-pharmacologic intervention research should test the effects of CBT interventions on pain and opioid consumption among patients with SCD.

Lastly, the findings of aim 4 support positive relationships among centrally-mediated S.P.A.C.E. symptoms and pain interference. Future non-opioid and non-pharmacologic intervention studies should consider conducting mediation analyses of S.P.A.C.E. symptoms on pain. The identification of S.P.A.C.E. mediators could guide the inclusion of specific cognitive and/or behavioral strategies that will effectively treat S.P.A.C.E. symptoms and subsequently reduce pain.

Recommendations for Clinical Practice

Our findings also have implications for clinical practice. The results of this study suggest that centralized pain influences pain and opioid consumption. Based on this evidence, we recommend routine screening of centralized pain among patients with SCD. Routine screening methods should incorporate standardized measures such as a body map or the ACR 2011 Fibromyalgia Survey Criteria to quantify widespread pain and centralized pain. Clinical assessment of centralized pain can be used to identify patients who may be more likely to experience opioid non-responsiveness and pain that impacts functioning (i.e., social, emotional, and physical functioning). Further, assessments of centralized pain can guide referrals to specialists (e.g., palliative care providers). Ultimately, targeted treatment of centralized pain may reduce pain and opioid use as well as improve function and quality of like among patients with SCD.

Conclusions

Limited research has evaluated multidimensional physiological and psychological factors, pain, and opioid consumption among patients with SCD. In this prospective, predictive, correlational study, we described the incidence and severity of several centrally-mediated symptoms and evaluated their co-occurrence with pain and opioid consumption, Further, we evaluated the predictive relationships among centrally-mediated symptoms, centralized pain, pain catastrophizing, opioid consumption, and pain interference. Our study demonstrated the predictive relationships among centralized pain, pain severity and opioid consumption. Our findings should be interpreted with caution due to our small sample size, low symptom severity, and suboptimal data completion rates. Individualized assessment of centralized pain can facilitate the recommendation of appropriate non-pharmacologic pain management strategies. Improved centralized pain management may ultimately lead to reductions in pain and opioid use and improvements in function and quality of life among patients with SCD.

References

Arnold, L. M., Keck, P. E., & Welge, J. A. (2000). Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics*, *41*(2), 104–113. https://doi.org/10.1176/appi.psy.41.2.104

Arnold, L. M., Lu, Y., Crofford, L. J., Wohlreich, M., Detke, M. J., Iyengar, S., & Goldstein, D. J. (2004). A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis and Rheumatism*, *50*(9), 2974–2984. https://doi.org/10.1002/art.20485

Arnold, L. M., Rosen, A., Pritchett, Y. L., D'Souza, D. N., Goldstein, D. J., Iyengar, S., & Wernicke, J. F. (2005). A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*, *119*(1–3), 5–15. https://doi.org/10.1016/j.pain.2005.06.031

Adam, S. S., Flahiff, C. M., Kamble, S., Telen, M. J., Reed, S. D., & De Castro, L. M. (2017). Depression, quality of life, and medical resource utilization in sickle cell disease. *Blood Advances*, *1*(23), 1983–1992. https://doi.org/10.1182/bloodadvances.2017006940 [doi]

Ameringer, S., Elswick Jr, R. K., & Smith, W. (2014). Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing*, *31*(1), 6–17. https://doi.org/10.1177/1043454213514632 [doi]

Bakshi, N., Lukombo, I., Belfer, I., & Krishnamurti, L. (2018). Pain catastrophizing is associated with poorer health-related quality of life in pediatric patients with sickle cell disease. *Journal of Pain Research*, 947–953.

Bakshi, N., Lukombo, I., Shnol, H., Belfer, I., & Krishnamurti, L. (2017). Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *The Journal of Pain*, *18*(10), 1216–1228. https://doi.org/S1526-5900(17)30599-0 [pii]

Barakat, L P, Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Barakat, Lamia P., Schwartz, L. A., Salamon, K. S., & Radcliffe, J. (2010). A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *32*(7), 540–547. https://doi.org/10.1097/MPH.0b013e3181e793f9

Bediako, S. M., Lanzkron, S., Diener-West, M., Onojobi, G., Beach, M. C., & Haywood, C. (2016). The Measure of Sickle Cell Stigma: Initial findings from the Improving Patient Outcomes through Respect and Trust study. *Journal of Health Psychology*, *21*(5), 808–820. https://doi.org/10.1177/1359105314539530

Benton, T. D., Ifeagwu, J. A., & Smith-Whitley, K. (2007). Anxiety and depression in children and adolescents with sickle cell disease. *Current Psychiatry Reports*, *9*(2), 114–121.

Brandow, A. M., Stucky, C. L., Hillery, C. A., Hoffmann, R. G., & Panepinto, J. A. (2013). Patients with sickle cell disease have increased sensitivity to cold and heat. *American Journal of Hematology*. https://doi.org/10.1002/ajh.23341

Brummett, C. M., Janda, A. M., Schueller, C. M., Tsodikov, A., Morris, M., Williams, D. A., & Clauw, D. J. (2013). Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology*, *119*(6), 1434–1443. https://doi.org/10.1097/ALN.0b013e3182a8eb1f [doi]

Büssing, A., Ostermann, T., Lüdtke, R., & Michalsen, A. (2012). Effects of yoga interventions on pain and pain-associated disability: A meta-analysis. *Journal of Pain*, *13*(1), 1–9. https://doi.org/10.1016/j.jpain.2011.10.001

Campbell, C. M., Kronfli, T., Buenaver, L. F., Smith, M. T., Haythornthwaite, J. A., & Edwards, R. R. (2011). Situational vs. dispositional measurement of catastrophizing: Associations. *J Pain*, *11*(5), 443–453. https://doi.org/10.1016/j.jpain.2009.08.009.Situational

Campbell, C. M., Moscou-Jackson, G., Carroll, C. P., Kiley, K., Haywood, C., Lanzkron, S., … Haythornthwaite, J. A. (2016). An Evaluation of Central Sensitization in Patients With Sickle Cell Disease. *The Journal of Pain*, *17*(5), 617–627. https://doi.org/10.1016/j.jpain.2016.01.475

Carroll, C. P., Lanzkron, S., Haywood, C. J., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016a). Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease. *American Journal of Preventive Medicine*, *51*(1 Suppl 1), S69-77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, C. P., Lanzkron, S., Haywood, C., Kiley, K., Pejsa, M., Moscou-Jackson, G., … Campbell, C. M. (2016b). Chronic opioid therapy and central sensitization in sickle cell disease. *American Journal of Preventive Medicine*, *51*(1), S69–S77. https://doi.org/10.1016/j.amepre.2016.02.012

Carroll, P. C., Haywood, C., Hoot, M. R., & Lanzkron, S. (2013). A preliminary study of psychiatric, familial, and medical characteristics of high-utilizing sickle cell disease patients. *Clinical Journal of Pain*, *29*(4), 317–323. https://doi.org/10.1097/AJP.0b013e3182579b87

Carter, B., Lambrenos, K., & Thursfield, J. (2002). A pain workshop: an approach to eliciting the views of young people with chronic pain. *Journal of Clinical Nursing*, *11*(6), 753–762.

Cassisi, G., Sarzi-Puttini, P., Casale, R., Cazzola, M., Boccassini, L., Atzeni, F., & Stisi, S. (2014). Pain in fibromyalgia and related conditions. *Reumatismo*, *66*(1), 72–86. https://doi.org/10.4081/reumatismo.2014.767

Corli, O., Roberto, A., Bennett, M. I., Galli, F., Corsi, N., Rulli, E., & Antonione, R. (2017). Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Practice*. https://doi.org/10.1111/papr.12669 [doi]

Daniel, L. C., Grant, M., Kothare, S. V, Dampier, C., & Barakat, L. P. (2010). Sleep Patterns in

Pediatric Sickle Cell Disease. *Pediatr Blood Cancer*, (October 2009), 501–507. https://doi.org/10.1002/pbc

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2017). The SPADE Symptom Cluster in Primary Care Patients with Chronic Pain. *Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286.The

Ezenwa, M. O., Yao, Y., Engeland, C. G., Molokie, R. E., Wang, Z. J., Suarez, M. L., & Wilkie, D. J. (2016). A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *Journal of Advanced Nursing*, *72*(6), 1452–1463. https://doi.org/10.1111/jan.12895

Ford, J. D., Grasso, D. J., Jones, S., Works, T., & Andemariam, B. (2017). Interpersonal Violence Exposure and Chronic Pain in Adult Sickle Cell Patients. *Journal of Interpersonal Violence*, 886260517691521. https://doi.org/10.1177/0886260517691521

Forgeron, P. A., King, S., Stinson, J. N., McGrath, P. J., MacDonald, A. J., & Chambers, C. T. (2010). Social functioning and peer relationships in children and adolescents with chronic pain: A systematic review. *Pain Research and Management*, *15*(1), 27–41. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-77950464526&partnerID=40&md5=1b217295f888cc94f5cc4d05615801ae

Grattan, A., Sullivan, M. D., Saunders, K. W., Campbell, C. I., & Von Korff, M. R. (2012). Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Annals of Family Medicine*, *10*(4), 304–311. https://doi.org/10.1370/afm.1371

Hanks, G. W., & Forbes, K. (1997). Opioid responsiveness. *Acta Anaesthesiologica Scandinavica*, *41*(1 Pt 2), 154–158.

Hassett, A. L., & Williams, D. A. (2011). Non-pharmacological treatment of chronic widespread musculoskeletal pain. *Best Practice & Research. Clinical Rheumatology*, *25*(2), 299–309. https://doi.org/10.1016/j.berh.2011.01.005

Hauser, W, Kosseva, M., Uceyler, N., Klose, P., & Sommer, C. (2011). Emotional, physical, and sexual abuse in fibromyalgia syndrome: a systematic review with meta-analysis. *Arthritis Care & Research*, *63*(6), 808–820. https://doi.org/10.1002/acr.20328 [doi]

Hauser, Winfried, Bernardy, K., Arnold, B., Offenbacher, M., & Schiltenwolf, M. (2009). Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis and Rheumatism*, *61*(2), 216–224. https://doi.org/10.1002/art.24276

Holtzman, S., Newth, S., & Delongis, A. (2004). The role of social support in coping with daily pain among patients with rheumatoid arthritis. *Journal of Health Psychology*, *9*(5), 677–695. https://doi.org/10.1177/1359105304045381

Jacob, E, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*, *37*(3), 185–189. https://doi.org/10.1097/MPH.0000000000000214 [doi]

Jacob, Eufemia, Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). *Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease*. *J Pediatr Hematol Oncol* (Vol. 37). Retrieved from www.jpho-online.com

Janda, A. M., As-Sanie, S., Rajala, B., Tsodikov, A., Moser, S. E., Clauw, D. J., & Brummett, C. M. (2015). Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology*, *122*(5), 1103–1111. https://doi.org/10.1097/ALN.0000000000000637 [doi]

Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary Care Companion for CNS Disorders*, *13*(2), 10.4088/PCC.10m01063. https://doi.org/10.4088/PCC.10m01063 [doi]

Kanzawa-Lee, G. A., Knoerl, R., Williams, D. A., Clauw, D. J., Bridges, C. M., Harte, S. E., … Lavoie Smith, E. M. (2018). Childhood Trauma Predicts Cancer Treatment-Related Pain in Breast Cancer Survivors. *Cancer Nursing*. https://doi.org/10.1097/NCC.0000000000000687

Knoerl, R, Lavoie Smith, E. M., & Weisberg, J. (2015). Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. *Western Journal of Nursing Research*, (Journal Article). https://doi.org/0193945915615869 [pii]

Knoerl, Robert, Chornoby, Z., & Smith, E. M. L. (2018). Estimating the Frequency , Severity , and Clustering of SPADE Symptoms in Chronic Painful Chemotherapy- Induced Peripheral Neuropathy. *Pain Management Nursing*, *19*(4), 354–365. https://doi.org/10.1016/j.pmn.2018.01.001

Knoerl, Robert, Lavoie Smith, E. M., & Weisberg, J. (2016). Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. *Western Journal of Nursing Research*, *38*(5), 596–628. https://doi.org/10.1177/0193945915615869

Lai, H. H., Jemielita, T., Sutcliffe, S., Bradley, C. S., Naliboff, B., Williams, D. A., … Landis, J. R. (2017). Characterization of Whole Body Pain in Urological Chronic Pelvic Pain Syndrome at Baseline: A MAPP Research Network Study. *The Journal of Urology*, *198*(3), 622–631. https://doi.org/10.1016/j.juro.2017.03.132

Laurence, B., George, D., Woods, D., & Baltimore, D. (2006). *Association between Elevated Depressive Symptoms and Clinical Disease Severity in African-American Adults with Sickle Cell Disease*.

Lemanek, K. L., Ranalli, M., & Lukens, C. (2009). A randomized controlled trial of massage therapy in children with sickle cell disease. *Journal of Pediatric Psychology*, *34*(10), 1091–1096. https://doi.org/10.1093/jpepsy/jsp015

Levenson, J L, McClish, D. K., Dahman, B. A., Bovbjerg, V. E., de A Citero, V., Penberthy, L. T., … Smith, W. R. (2008). Depression and anxiety in adults with sickle cell disease: the PiSCES project. *Psychosomatic Medicine*, *70*(2), 192–196. https://doi.org/PSY.0b013e31815ff5c5 [pii]

Levenson, James L., McClish, D. K., Dahman, B. A., Bovbjerg, V. E., De A. Citero, V., Penberthy, L. T., … Smith, W. R. (2008). Depression and anxiety in adults with sickle cell

disease: The PiSCES project. *Psychosomatic Medicine*, *70*(2), 192–196. https://doi.org/10.1097/PSY.0b013e31815ff5c5

Maletic, V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Frontiers in Bioscience*, *14*, 5291–5338.

Mann-Jiles, V., Thompson, K., & Lester, J. (2015). Sleep impairment and insomnia in sickle cell disease: A retrospective chart review of clinical and psychological indicators. *Journal of the American Association of Nurse Practitioners*, *27*(8), 441–449. https://doi.org/10.1002/2327-6924.12212

Martin, S. R., Cohen, L. L., Mougianis, I., Griffin, A., Sil, S., & Dampier, C. (2018). Stigma and Pain in Adolescents Hospitalized for Sickle Cell Vasoocclusive Pain Episodes. *The Clinical Journal of Pain*, *34*(5), 438–444. https://doi.org/10.1097/AJP.0000000000000553 [doi]

McClish, D. K., Smith, W. R., Dahman, B. A., Levenson, J. L., Roberts, J. D., Penberthy, L. T., … Bovbjerg, V. E. (2009). Pain site frequency and location in sickle cell disease: The PiSCES project. *Pain*, *145*(1–2), 246–251. https://doi.org/10.1016/j.pain.2009.06.029

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: An examination in a nationally representative sample. *Pain*, *106*(1–2), 127–133. https://doi.org/10.1016/S0304-3959(03)00301-4

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain*, *111*(1–2), 77–83. https://doi.org/10.1016/j.pain.2004.06.002

Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., … Carroll, A. (2017). A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *Journal of Pain and Symptom Management*, *53*(6), 1026–1034. https://doi.org/10.1016/j.jpainsymman.2016.12.351

Moscou-Jackson, G., Finan, P. H., Campbell, C. M., Smyth, J. M., & Haythornthwaite, J. A. (2015). The effect of sleep continuity on pain in adults with sickle cell disease. *Journal of Pain*, *16*(6), 587–593. https://doi.org/10.1016/j.jpain.2015.03.010

O'Malley, P. G., Balden, E., Tomkins, G., Santoro, J., Kroenke, K., & Jackson, J. L. (2000). Treatment of fibromyalgia with antidepressants: A meta-analysis. *Journal of General Internal Medicine*, *15*(9), 659–666. https://doi.org/10.1046/j.1525-1497.2000.06279.x

Oram, S., Ostrovschi, N. V, Gorceag, V. I., Hotineanu, M. A., Gorceag, L., Trigub, C., & Abas, M. (2012). Physical health symptoms reported by trafficked women receiving post-trafficking support in Moldova: prevalence, severity and associated factors. *BMC Women's Health*, *12*, 20. https://doi.org/10.1186/1472-6874-12-20

Ozer, C., Yengil, E., Acipayam, C., & Kokacya, M. H. (2014). Relationship between depression, anxiety, quality of life and vaso-occlusive crisis in adolescents with sickle cell disease. *Acta Medica Mediterranea*, *30*(2), 335–339. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84898471979&partnerID=40&md5=7d617897f2596c49705119a3d2b85bcf

Phillips, K, & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states--maybe it is

all in their head. *Best Practice & Research.Clinical Rheumatology*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005 [doi]

Phillips, Kristine, & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states-maybe it is all in their head. *Best Pract Res Clin Rheumatol*, *25*(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005

Platt, O. S., Thorington, B. D., Brambilla, D. J., Milner, P. F., Rosse, W. F., Vichinsky, E., & Kinney, T. R. (1991). Pain in sickle cell disease. Rates and risk factors. *The New England Journal of Medicine*, *325*(1), 11–16. https://doi.org/10.1056/NEJM199107043250103 [doi]

Schatz, J., Schlenz, A. M., McClellan, C. B., Puffer, E. S., Hardy, S., Pfeiffer, M., & Roberts, C. W. (2015). Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *The Clinical Journal of Pain*, *31*(6), 536–547. https://doi.org/10.1097/AJP.0000000000000183 [doi]

Schofferman, J., Anderson, D., Hines, R., Smith, G., & Keane, G. (1993). Childhood psychological trauma and chronic refractory low-back pain. *The Clinical Journal of Pain*, *9*(4), 260–265.

Sharma, S., Efi, J. T., Knupp, C., Kadali, R., Liles, D., & Shiue, K. (2015). Sleep Disorders in Adult Sickle Cell Patients, *11*(3), 1–5.

Shattuck, E. C., & Muehlenbein, M. P. (2016). Towards an integrative picture of human sickness behavior. *Brain, Behavior, and Immunity*, *57*, 255–262. https://doi.org/10.1016/j.bbi.2016.05.002

Skljarevski, V., Desaiah, D., Liu-Seifert, H., Zhang, Q., Chappell, A. S., Detke, M. J., … Backonja, M. (2010). Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine*, *35*(13), E578-85. https://doi.org/10.1097/BRS.0b013e3181d3cef6

Slade, G. D., Smith, S. B., Zaykin, D. V, Tchivileva, I. E., Gibson, D. G., Yuryev, A., … Diatchenko, L. (2013). Facial pain with localized and widespread manifestations: separate pathways of vulnerability. *Pain*, *154*(11), 2335–2343. https://doi.org/10.1016/j.pain.2013.07.009

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., … Oncology, A. for C. T. in. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama*, *309*(13), 1359–1367. https://doi.org/10.1001/jama.2013.2813

Smith, W. R., Penberthy, L. T., Bovbjerg, V. E., Mcclish, D. K., & Roberts, J. D. (2008). Daily Assessment of Pain in Adults with Sickle Cell Disease. *Annals of Internal Medicine*, *148*, 94–101. https://doi.org/10.7326/0003-4819-148-2-200801150-00004

Snelling, J. (1994). The effect of chronic pain on the family unit. *Journal of Advanced Nursing*, *19*(3), 543–551.

Spiegel, D. R., Chatterjee, A., McCroskey, A. L., Ahmadi, T., Simmelink, D., Oldfield 4th, E. C., … Raulli, O. (2015). A Review of Select Centralized Pain Syndromes: Relationship With Childhood Sexual Abuse, Opiate Prescribing, and Treatment Implications for the Primary Care Physician. *Health Services Research and Managerial Epidemiology*, *2*,

2333392814567920-Dec. https://doi.org/10.1177/2333392814567920 [doi]

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D. B., & Paulus, M. P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry*, *65*(11), 1275–1284. https://doi.org/10.1001/archpsyc.65.11.1275

Thomas, L. S., Stephenson, N., Swanson, M., Jesse, D. E., & Brown, S. (2013). A pilot study: the effect of healing touch on anxiety, stress, pain, pain medication usage, and physiological measures in hospitalized sickle cell disease adults experiencing a vaso-occlusive pain episode. *Journal of Holistic Nursing*, *31*(4), 234–247. https://doi.org/10.1177/0898010113491631

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., … Watanabe, M. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The Journal of Pain : Official Journal of the American Pain Society*, *9*(10), 883–891. https://doi.org/10.1016/j.jpain.2008.05.005

Verdu, B., Decosterd, I., Buclin, T., Stiefel, F., & Berney, A. (2008). Antidepressants for the treatment of chronic pain. Drugs, 68(18), 2611–2632. Retrieved from https://link.springer.com/content/pdf/10.2165%2F0003495-200868180-00007.pdf

Vacca Jr, V. M., & Blank, L. (2017). Sickle cell disease: Where are we now? *Nursing*, *47*(4), 26–34. https://doi.org/10.1097/01.NURSE.0000513609.79270.74 [doi]

Wasserman, R. A., Brummett, C. M., Goesling, J., Tsodikov, A., & Hassett, A. L. (2014). Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Regional Anesthesia and Pain Medicine*, *39*(1), 13–17. https://doi.org/10.1097/AAP.0000000000000024 [doi]

Zaza, C., & Baine, N. (2002). Cancer pain and psychosocial factors: a critical review of the literature. *Journal of Pain and Symptom Management*, *24*(5), 526–542.

Zempsky, W. T., Wakefield, E. O., Santanelli, J. P., New, T., Smith-Whitley, K., Casella, J. F., & Palermo, T. M. (2017). Widespread Pain Among Youth With Sickle Cell Disease Hospitalized With Vasoocclusive Pain: A Different Clinical Phenotype? *The Clinical Journal of Pain*, *33*(4), 335–339. https://doi.org/10.1097/AJP.0000000000000403 [doi]

APPENDICES

Appendix A-1

Pain Influencing Factors in Patients with SCD

Table 19

Pain Influencing Factors in Patients with SCD

Author	Study type	Sample and Setting	Influencing factor(s)	Pain Measures	Influencing Factor Results	Limitations
(Bakshi et al., 2018)	Cross-sectional	*N*=47 adults with SCD *n*=33 those with pain 3 or more days per week • Median age: 35 years *n*=14 those with pain <3 days per week • Median age: 36.5 years Setting: regional and national SCD conferences and local SCD clinics	Physiological: age, sex Psychological: depression, anxiety	Pain on 3 or more days per week (dichotomous variable) PROMIS Pain interference	There was no significant difference between those with pain 3 or more days per week and those with pain <3 days per week based on age and sex. Statistically significant differences were found in depression (52 vs. 43.35; p=0.029) and anxiety (55.6 vs. 48.8; p=0.0178) scores among those who reported pain on 3 or more days per week vs. those who did not. When adjusting for age and sex, pain on 3 or more days per week significantly predicted greater anxiety (p<0.05).	Sample included 79% women Pain outcome dichotomous variable Those with who did not adhere to filling out PRO measures were significantly younger than those that did not No corrections for multiple comparisons No power analysis reported

(Finan et al., 2018)	Longitudinal	*N*=45 adults with SCD • Mean age: 37.49 years Setting: Sample recruited from local SCD clinics and from posted flyers and advertisements	Psychological: catastrophization	Daily diary • Numeric Rating Scale • Dichotomous VOC variable • Pain Catastrophizing Scale	Daily levels of pain (p= 0.006) and catastrophizing ($p < 0.001$) were significantly associated with daily levels of short-acting opioid use. Daily pain and catastrophizing were not associated with long-acting opioid use.	Patients in the sample reported low levels of pain, on average No corrections for multiple comparisons No comparison between those with and without centralized pain
(Martin et al., 2018)	Cross-sectional	*N*=92 • Mean age: 15.02 years Setting: Inpatient unit at children's hospital	Situational: sickle cell stigma	PROMIS Pain Interference Scale Pain Intensity: Numeric Pain Rating Scale Change in pain: Pain at discharge subtracted from pain at admission	Higher stigma was significantly associated with increased pain interference ($p \leq 0.01$) and less change in pain scores ($p \leq 0.05$) while in the hospital.	Preliminary data from newly developed PRO stigma measure No comparison between those with and without centralized pain
(Antunes et al., 2017)	Cross-sectional	*N*=56 with SCD *n*=14 with NP • Mean age: 22.7 years *n*=42 without NP • Mean age: 19.8 years	Physiological: sex, age	Leeds assessment of neuropathic symptoms and signs (LANSS) scale; scores of > 11 were	Patients with NP were significantly older than those without NP ($p<0.05$). There were no significant differences based on sex between groups.	Evidence suggests that total scores <12 on LANSS scale suggests unlikely neuropathic pain(Rutherford,

		Setting: Brazil outpatient university clinic		classified as evidence of neuropathic pain (NP)		Nixon, Brown, Briggs, & Horton, 2016) No power analysis reported Small sample size within the NP group

(Bakshi et al., 2017)	Case-control	*N*=52 *n*=29 with SCD • Median age: 15 years *n*=29 controls Setting: large academic children's hospital	Physiological: age, sex Psychological: depression, anxiety, catastrophization	QST: • Pressure pain threshold • Mechanical detection threshold • Thermal detection thresholds • Thermal pain thresholds PROMIS Pain Intensity Scale Gracely Box Scale: Pain intensity and unpleasantness VOC incidence during 3-years prior to QST testing	Age was significantly associated with pressure (p=0.004) and heat pain tolerance (p=0.028) in patients with SCD. In those with SCD, increased age was associated with lower mechanical temporal summation (p=0.045). In patients with SCD, male sex was significantly associated with higher heat detection threshold (p=0.023). Depressive symptoms (p<0.01) and anxiety (p<0.01) were associated with higher cold pain thresholds. However, depressive symptoms were significantly associated with lower heat pain thresholds (p<0.01) in those with SCD. Catastrophization scores were associated with higher cold pain thresholds (p<0.01)	No corrections for multiple comparisons Possible selection bias since participants needed to come in for separate QST appointment Authors reported relatively low incidence of pain within the sample No comparison between those with and without centralized pain

					and lower mechanical pain tolerance (p<0.01) in those with SCD. In multiple regression models adjusted for age and sex, increased VOC was independently associated with increased heat pain thresholds (p<0.01) and tolerance (p<0.05), decreased mechanical temporal summation (p<0.05), and decreased cold detection thresholds (p<0.01).	
(Ford et al., 2017)	Cohort	*N*=50 *n*=34 exposed to trauma • Mean age: 34.9 years *n*=16 nonexposed • Mean age: 24.9 years Setting: University of Connecticut Health Center's adult comprehensive SCD program	Psychological: depression, anxiety Situational: trauma exposure (interpersonal violence)	Self-reported chronic pain: presence of moderate to severe pain on more than 50% of days in the last 6 months Daily opiate use: prescription for long- or short-acting oral, subcutaneous,	While controlling for age and depression, patients who reported interpersonal violence were nearly 5x more likely to self-report chronic pain (p=0.05) and to take a daily opiate (p=0.023). Self-reported chronic pain was not significantly associated with depression and anxiety.	Dichotomous outcome measure Significant differences between those exposed and unexposed to interpersonal violence could have influenced the incidence of chronic pain

				or transdermal opiates prescribed for use on a daily basis from medical record		Opiate use was based on prescriptions and not self-reported opiate use No power analysis reported No corrections for multiple comparisons described
(Moody et al., 2017)	RCT	*N*=73 with SCD admitted to hospital with pain ≥ 7 *n*=35 yoga group • Mean age: 15 years *n*=35 control group • Mean age: 14 years Setting: Children's hospital in Bronx, NY	Psychological: anxiety	FACES pain scale	There were no significant differences in anxiety between groups.	No blinding No comparison between those with and without centralized pain Evidence suggests this Intervention targets central pain mechanisms,

		Intervention: yoga intervention (n=35) vs attention control (n=35); Intervention delivered by instructor for 30 minutes daily Monday through Friday. Four elements of yoga were incorporated into the intervention: mindfulness, asanas, breathing exercises, and guided relaxation.				but it was delivered among those experiencing acute VOC

(Zempsky et al., 2017)	Cross-sectional	*N*=156 with SCD *n*=34 widespread pain group • Mean age: 15.56 years *n*= 122 without widespread pain • Mean age: 15.72 years Patients with SCD ages 7-21 Setting: 4 children's hospitals; inpatient	Physiological: SCD genotype, sex, age	Pain location: Adolescent pediatric pain tool Widespread Pain: WSP Index Pain Intensity: Average pain score during hospitalization	No significant differences between patients with and without widespread pain among sex, age, and SCD genotype.	Post hoc analysis No corrections for multiple comparisons Small sample size within the widespread pain group No power analysis reported

(Bediako et al., 2016)	Cross-sectional	*N*=262 • Mean age: 34.5 years Setting: two comprehensive SCD centers in the Baltimore/Washington are	Situational: sickle cell stigma	Acute care service utilization: # of times in ED or infusion clinic for pain in the past year (self-report) Hospital admissions: # of hospital admissions for pain in the past year (self-report)	Sickle cell stigma factors including social exclusion ($p<0.01$), internalized stigma ($p<0.05$), and expected discrimination ($p<0.05$) were significantly associated with acute care visits for SCD pain.	Self-reported health care utilization and hospital admission assessments could be subject to recall bias No corrections for multiple comparisons described No power analysis reported

(Carroll et al., 2016)	Longitudinal	*N*=83 with SCD *n*=54 no chronic opioid therapy (COT) • Median age: 38 years *n*=29 COT • Median age: 40.6 years Setting: Sickle Cell Center for Adults at Johns Hopkins	Physiological: genotype, sex, age Psychological: depression	QST: • Heat pain thresholds • Pressure pain thresholds • Temporal summation Brief Pain Inventory Daily pain diary: • Pain intensity (0-100) Pain interference	Patients with chronic opioid therapy had significantly greater depression compared to those without (20.2 vs. 12; $p<0.01$). There were no significant differences between those with and without chronic opioid therapy regarding genotype, sex, and age.	Lack of information regarding pain prior to COT, prior opioid exposure, and duration of COT prior to the study Reduced power for some analyses due to small sample in COT group

(Campbell et al., 2016)	Longitudinal	*n*=17 with low central sensitization (CS) • Mean age: 35.6 years *n*=21 with high CS • Mean age: 42.8 years Setting: Sickle Cell Center for Adults at Johns Hopkins	Physiological: sleep Psychological: depression, catastrophization	QST: • Heat Pain Threshold • Pressure Pain Threshold • Temporal summation • Conditioned Pain Modulation Pain Intensity following QST: 0-100 scale Daily pain diary: • Pain intensity: 0-100 • Pain interference Presence of VOC	Patients in the high CS group reported significantly poorer sleep continuity on all components of the Pittsburgh Sleep Quality Index (all $p<$ 0.05). Also, those in the high CS group reported increased insomnia (p=0.005). There were no significant differences between the high and low CS groups in genotype, age, sex, depressive symptoms, and pain catastrophizing.	Patient report of # of VOC Pain interference measure not reliable and valid No power analysis reported Small sample size within the NP group Strict inclusion criteria

(Schlenz, Schatz, & Roberts, 2016)	Cross-sectional	*N*=76 • Mean age: 14.05 years Setting: Children's Center for Cancer and Blood Disorders (CCBD) in South Carolina	Physiological: genotype	Pain History Interview (parent and child retrospective reports): • Pain Intensity • Pain Duration • Pain Frequency Health service utilization (previous 12 months)	Patients with high risk genotypes (HbSS and HbSβ^0 had higher pain intensity (7.48 vs. 6.58; $p<0.05$) and health care utilization (4.02 vs. 2.08; $p<0.05$) ratings than those with low risk genotypes (HbSC and HbSβ^+).	Pain History Interview retrospective assessments could be subject to recall bias Small sample reduced power
(Sil et al., 2016)	Cross-sectional	*N*=100 (*n*=40 chronic pain, *n*=40 episodic pain, *n*=20 no pain) • Mean age: 13.54 years Setting: outpatient sickle cell clinic	Physiological: genotype, sex, age Psychological: depression, catastrophizing	Pain intensity: average pain in last 2 weeks Pain frequency: # of pain days in last month (patient and parent report) Health care utilization: number of hospitalization	There were no significant differences in genotype and sex among the three groups. Patients in the chronic pain group were significantly older than those in the no SCD pain group (14.41 vs. 11.62). Chronic pain group had higher levels of depressive symptoms than those in the no pain group (13.40 vs.	Possibility for recall bias based on pain outcome measures Definition for chronic pain was based on pain frequency and not central pain mechanisms

				s, and ED visits related to pain within last year	4.35; $p<0.001$) and the episodic pain group (13.40 vs. 9.13; $p<0.001$). Also, the no pain group had significantly less levels of pain catastrophizing than those in the episodic pain group (17.85 vs. 24.98; $p<0.01$) and the chronic pain group (17.85 vs. 28.13; $p<0.01$). No significant differences were found in catastrophizing scores between the chronic and episodic groups.	

(Jacob et al., 2015)	Cross-sectional	*N*=48 children with SCD *n*=35 normal QST • Mean age: 13.9 years *n*=13 abnormal QST • Mean age: 12.8 years Setting: Sickle Cell Disease Foundation of California	Physiological: genotype, sex, age Psychological: depression, anxiety	QST: • Nonpainful mechanical stimulus • Painful mechanical stimulus • Thermal detection thresholds Pain Intensity: Visual Analogue Scale	Patients with normal QST did not differ from those with abnormal results based on genotype, sex, age, depression, and anxiety.	Only one body site was analyzed using QST No power analysis reported No corrections for multiple comparisons Small sample size within the abnormal QST group

(Moscou-Jackson et al., 2015)	Longitudinal	*N*=75 • Mean age: 35.5 years Setting: SCD clinics	Physiological: sleep	Daily pain diary: • Pain intensity: 0-100 • Pain interference • Presence of VOC	Pain severity significantly correlated with the following sleep continuity variables: total sleep time (p<0.01), mean time in bed (p<0.05), mean sleep onset latency (p<0.01), mean wake after sleep onset (p<0.01), and mean sleep efficiency (p<0.01). Lower total sleep time (p<0.001), lower sleep efficiency (p=0.02), lower time in bed (p=0.01), and higher wake after sleep onset (p<0.001) all predicted increased next-day pain. For every 30-minute decrease in wake after sleep onset, next-day pain severity was estimated to be lower by 0.60 points.	Pain interference measure not reliable and valid No power analysis reported Strict inclusion criteria No comparison between those with and without centralized pain

(Ameringer et al., 2014)	Cross-sectional	*N*=60 with SCD • Mean age: 22.5 years	Physiological: fatigue	Brief Pain Inventory	Fatigue scores assessed via the Brief Fatigue Inventory were significantly associated with worst pain, average pain, and pain interference (all $p \leq 0.001$).	Setting not described
(Brandow et al., 2014)	Cross-sectional	*N*=56 with SCD • Median age: 20.3 Setting: Outpatient sickle cell center	Physiological: sex, age	PainDETECT	Age was positive correlated with total PainDETECT score (p=0.001). Females had significantly higher scores than males (13 vs. 8.4; p=0.04).	Descriptive design with one PRO measure
(Graves & Jacob, 2014)	Cross-sectional	*N*=66 *n*=39 children • Mean age: 11.9 years *n*=27 adolescents • Mean age: 15.5 years Setting: Sickle Cell Disease Foundation of California	Physiological: age, sex, sleep Psychological: catastrophizing	Pain Intensity: electronic Visual Analog Scale Pain Frequency: # of pain episodes in the previous 12 months that required hospitalization (parent report)	There were significant negative correlations in males between worst pain severity and positive behavioral distraction (r= −0.432; p=0.01) and negative internalizing/ catastrophizing (r= −0.457; p=0.049), but not in females. There were no significant differences in pain	Parent report pain frequency measurement may be subject to recall bias Convenience sampling was used which could reduce generalizability of findings

				Pediatric Pain Coping Questionnaire	intensity or frequency based on age and gender. There were no significant differences in sleep scores based on pain intensity and pain severity.	No corrections for multiple comparisons described No power analysis reported No comparison between those with and without centralized pain
(Wallen et al., 2014)	Cross-sectional	*N*= 328 with SCD • Median age: 34 years Setting: NIH Clinical Center	Physiological: sleep Psychological: depression	# of VOC within the past 12 months	Increased sleep disturbance was significantly associated with increased pain frequency (p=0.003) and health care utilization (p=<0.001). Mild/moderate pain was significantly associated with depression (p=0.001).	Potential recall bias with patient report of # of VOC Surveys were administered at two separate times during a larger parent study (at initiation and

						study follow-up).This variable was not controlled for among patients No comparison between those with and without centralized pain
(Brandow et al., 2013)	Cross-sectional	*n*=55 with SCD • Mean age: 15.4 *n*=57 controls • Mean age: 16.3 Setting: Wisconsin Sickle Cell Center	Physiological: sex, age	QST: • Thermal pain thresholds • Thermal detection thresholds • Mechanical detection threshold Mechanical pain threshold	Older age was significantly associated with lower cold (p=0.02), heat (p=0.004), and mechanical (p=0.03) pain thresholds. There were no significant differences in sex.	

(Carroll et al., 2013)	Cross-sectional	*N*=56 with SCD *n*=29 high health service utilizers • Mean age: 28.6 years *n*=27 comparison group • Mean age: 38 years Setting: Sickle Cell Center for Adults at Johns Hopkins	Physiological: genotype, age Psychological: depression, Situational: trauma exposure, social support	High utilizers: 4 acute or emergency care visits within the past 12 months	Patients in the high health service utilizer group were significantly younger than the comparison group (p=0.002). No significant differences between high health service utilizers and the comparison group regarding genotype, depression, social support, trauma exposure.	All acute care or emergency visits were included, not solely ones for pain Low power due to small sample No corrections for multiple comparisons No comparison between those with and without centralized pain

(Thomas et al., 2013)	RCT	*N*=17 adults with SCD experiencing VOC • Mean age: 31.5 years Setting: Southeastern North Carolina Health Care System Intervention: Healing Touch with Music (HTM) (n=11) vs. Attention Control with Music (ACM) group (n=6); Intervention delivered over 30 minutes for four consecutive days	Psychological: anxiety	Numeric rating scale	There were no significant differences in anxiety between the intervention and control groups. Within-group comparisons showed that the control group had a significant reduction in anxiety from Day 1 to 4 (p=0.01).	Small sample reduced the power to detect differences between groups No comparison between those with and without centralized pain

(Jerrell et al., 2011)	Cohort	*N=2194* *n*=1017 depression cohort • Mean age of major depressive disorder diagnosis: 14.2 years *n*=1177 control cohort Setting: Medicaid claims data from South Carolina's Medicaid program	Psychological: depression	VOC pain visits per year	Those diagnosed with depression were more likely to have vaso-occlusive pain (OR = 1.06; 95% CI, 1.03–1.08; $p<0.0001$) than those in the control cohort.	No centrally-mediated covariates included in the regression models No comparison between those with and without centralized pain
(Brousseau et al., 2010)	Longitudinal	*N*= 21,112 with SCD • Age range: 1-65+ Setting: Emergency Department and inpatient units	Physiological: age	N/A	Patients ages 18-30 had the acute care encounters per year (3.61; 95% CI, 3.47-3.75) and re-hospitalization rates (28.4%; 95% CI, 27.8%- 29.0%) compared to all other age groups.	All ED visits and hospitalizations were included, not solely ones for pain No comparison between those with and without centralized pain

(Daniel et al., 2010)	Case control	*n*=54 parents of children with SCD • Mean age: 6.56 years *n*=52 healthy controls • Mean age: 6.71 years Setting: urban children's hospital	Physiological: sleep	Derived from medical record: • Health Utilization Score SCD Complications Score	SCD complications score was significantly correlated with reports of parasomnias (p= 0.003), sleep-disordered Breathing (p = 0.003), and the Total Sleep Problems score (p=0.021). The Healthcare Utilization summary score was also significantly correlated with the parasomnia subscale items (p= 0.021). SCD complications and health utilization scores did not significantly predict restless sleep and sleep-disordered breathing within regression models.	Parent reported sleep habits of children Some significant results were based on subscales rather than total sleep scale scores No corrections for multiple comparisons described
(Lemanek et al., 2009)	RCT	*N*=34 with SCD and their caregivers *n*=18 massage group • Mean age: 9.97 years *n*=16 control group	Psychological: depression, anxiety	Pediatric Pain Scale	After the 30-day study period, participants in the intervention group had significantly less depression (p=0.05), anxiety (p=0.01), and pain ratings (p=0.05) compared to the control group. There were no significant	Not blinded Lack of standardizatio n of intervention No comparison between those

		• Mean age: 11.55 years Setting: Sickle Cell Disease program at children's hospital Intervention: Massage group vs attention control group; massage therapist visited home weekly for 4 weeks and trained the caregiver how to give massages. Children received massages by caregiver between therapist days. Massage intervention lasted 30 days.			differences between groups based on health care utilization.	with and without centralized pain

(McClish et al., 2009)	Longitudinal cohort study	*N*=260 with SCD Patients with SCD • Mean age: 33.9 years Setting: specialty sickle cell clinics and community centers	Physiological: genotype, sex, age Psychological: Depression	Pain diary: • Pain intensity- 0-9 scale • Incidence of sickle cell crisis • Health service use • Body chart	Significant differences in multifocal pain based on age (p=0.0120) and depression (p=0.0111). There were no significant differences based on SCD genotype and sex.	Missing diary data not reported No description of how depression was identified Outcome measures not reliable and valid No comparison between those with and without centralized pain

Appendix A-2

Critical Appraisal for Pain Influencing Factors in SCD:

Randomized Controlled Trials

Table 20

Critical Appraisal for Pain Influencing Factors in SCD: Randomized Controlled Trials

Author	Randomized	Allocation concealed	Similar groups	Blinding	Groups treated identically	Follow -up	Analyzed within groups	Measures Reliable	Appropriate Statistics	Appropriate Design
(Moody et al., 2017)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
(Thomas et al., 2013)	Yes	?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
(Lemanek et al., 2009)	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No

Appendix A-3

Critical Appraisal for Pain Influencing Factors in SCD:

Case Control Studies

Table 21

Critical Appraisal for Pain Influencing Factors in SCD: Case Control Studies

Author	Similar groups	Appropriate matching	Same inclusion criteria	Measures reliable and valid	Confounders identified	Strategies to deal with confounders	Appropriate statistics
(Brandow et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(Daniel et al., 2010)	Yes	?	Yes	No	Yes	Yes	?
(Bakshi et al., 2017)	Yes	No	No	No	Yes	Yes	No

Appendix A-4

Critical Appraisal for Pain Influencing Factors in SCD:

Cross-Sectional Studies

Table 22

Critical Appraisal for Pain Influencing Factors in SCD: Cross-Sectional Studies

Author	Inclusion Defined	Sample and Setting Described	Exposure measure reliable and valid	Objective criteria for measuring condition	Confounders listed	Strategies to deal with confounders	Outcome measures reliable and valid	Appropriate statistics
(Bakshi et al., 2018)	Yes	Yes	Yes	Yes	Yes	Yes	No	No
(Martin et al., 2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(Antunes et al., 2017)	Yes	Yes	Yes	Yes	No	No	No	Missing power analysis
(Zempsky et al., 2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
(Bediako et al., 2016)	Yes	Yes	Yes	Yes	No	No	No	Missing power analysis

(Schlenz, Schatz, & Roberts, 2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	Reduced power
(Sil et al., 2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
(Jacob et al., 2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
(Ameringer et al., 2014)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
(Brandow et al., 2014)	Yes	Yes	Yes	Yes	No	No	Yes	Yes
(Graves & Jacob, 2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Missing power analysis
(Wallen et al., 2014)	Yes	Yes	Yes	Yes	No	No	No	Yes
(Carroll et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Appendix A-5

Critical Appraisal Pain Influencing Factors in SCD:

Cohort Studies

Table 23

Critical Appraisal Pain Influencing Factors in SCD: Cohort Studies

Author	Similar groups	Exposure measure standardized	Confounders identified	Strategies to deal with confounders	Measures reliable and valid	Follow-up time appropriate	Follow-up complete, or lack of follow-up explained	Strategies to address incomplete follow-up	Appropriate statistics
(Finan et al., 2018)	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
(Ford et al., 2017)	No	Yes	Yes	Yes	No	Yes	Yes	No	?
(Campbell et al., 2016)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Missing power analysis

(Carroll et al., 2016)	No	Yes	Yes	Yes	Yes	Yes	?	?	Reduced power
(Moscou-Jackson et al., 2015)	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Missing power analysis
(Jerrell et al., 2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(Brousseau et al., 2010)	N/A	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes
(McClish et al., 2009)	N/A	Yes	Yes	Yes	No	Yes	No	No	Yes