EXAMINATION OF SLEEP IN AFRICAN AMERICAN ADULTS WITH SICKLE CELL DISEASE

by
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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
June, 2015

ABSTRACT

Background: A growing body of research suggests that adults with sickle cell disease (SCD) experience sleep disturbances, specifically difficulty falling asleep and staying asleep, which are two symptoms of insomnia. Despite this evidence, there is a paucity of scientific literature that has systematically explored insomnia symptoms in this population. The present study addresses this gap by examining the prevalence, risk factors, and potential outcomes of insomnia symptoms, in community-dwelling adults with SCD.

Methods: This study was a secondary analysis of data from two prospective cohort studies of individuals with SCD. Participants were conveniently sampled from outpatient SCD clinics in the Baltimore-Washington Metropolitan area. Between datasets, the Insomnia Severity Index and a daily electronic diary were used to measure sleep characteristics and insomnia symptoms. Descriptive statistics, regression analyses, and multi-level modeling were used.

Datasets: Improving Patient Outcomes with Respect and Trust (IMPORT) and Clinical Implications of Pain Phenotypes in Sickle Cell Disease.

Results: Among 263 adults with SCD from the IMPORT study, 41% reported clinically relevant insomnia symptoms. Depression and pain were identified as independent statistical predictors of insomnia symptom severity. Using the Pain Phenotype cohort of 75 adults with SCD, a bidirectional relationship between sleep and pain was noted. Analyses of up to three months of daily electronic diaries revealed that short sleep duration, long sleep onset latency, and increased sleep fragmentation, were predictors of increased clinical pain in adults with SCD. Further, the analgesic benefit of longer sleep

duration was attenuated when sleep fragmentation was elevated. Finally, preliminary evidence using the IMPORT cohort suggested that insomnia symptom severity is associated with increased health care utilization.

Conclusions: Sleep disturbances, specifically insomnia symptoms, are prevalent among adults with SCD and are associated with depression and pain severity. Insomnia symptoms may also be associated with increased healthcare utilization. While a randomized control trial may be premature, clinicians working with this population should regularly assess for sleep disturbances and provided interventions that include treatment of depressive symptoms and pain as needed.

Advisor: Dr. Jerilyn Allen, RN, ScD, FAAN

DEDICATIONS

To the generations of Moscou women before me, thank you for paving the way and never letting me give up. To my grandma Dorothy, thank you for raising the strong Black women who became my role models. To my mom Kathy, thank you for always encouraging me to follow my dreams and providing priceless advice along the way. To my aunt Susie, thank you for being my academic inspiration and champion and for showing me that nursing is an awesome career.

Funding for this dissertation work was provided by:

National Institute of Nursing Research

Grant no. F31NR014598 (2013-2015)

and T32NR012704 (2011-2013)

Disclaimer:

The views expressed in this document are those of the author, and do not necessarily represent the official views of the National Institutes of Health.

ACKNOWLEDGMENTS

To start a dissertation, it takes a hope and a dream. To finish a dissertation it takes a lot of hard work, dedication, and the support of many. Thank you to ALL of the family, advisors, and mentors throughout my academic career who helped and encouraged me to start, progress through, and finish this dissertation. A special thank you to the individuals below who were extremely influential throughout the dissertation phase.

I would not have entered the PhD program, if it were not for Dr. Marie Nolan. As a baccalaureate student in the School of Nursing, Dr. Nolan, the then PhD program director, saw potential and encouraged me to pursue a PhD before even finishing my BSN. I will never forget her contacting me just weeks before I was scheduled to begin working as a clinical nurse in the hospital and offering me a position in the program with funding despite never even applying. While I didn't take her offer then, she planted the seed that started me on this journey.

The conception of this dissertation could not have been possible without my advisor and mentor, Dr. Jerilyn Allen, who gave me the article that inspired me to study adults with sickle cell disease. Dr. Allen always challenged me, dotted my T's and crossed my I's (when I could no longer see those details), and provided invaluable expertise and experience along the way.

Completing this dissertation could not have been possible or as exciting without the support of Drs. Carlton Haywood Jr, Sophie Lanzkron, and Jennifer Haythornthwaite, my sickle cell experts and mentors. Each of them made me excited to be a part of the sickle cell research community and their own work inspired and encouraged me to believe in the impact I could have on this patient population. This dissertation would also

not be possible without the IMPORT and Pain Phenotype Study principal investigators (Mary Catherine Beach, MD, Carlton Haywood Jr, PhD and Jennifer Haythornthwaite, PhD), the study team, and the participants, who envisioned the study, provided and collected the data, and allowed me use the data to complete this dissertation.

When going through the highs and lows of this process, I could always count on Dr. Michael Smith, my dissertation chair and sleep expert, for support. Dr. Smith unknowingly gave me permission to finish this dissertation and move on to the next phase of my doctoral career, which was extremely valuable advice that emotionally moved me forward and gave me the confidence to finish.

While important to have an advisor, sometimes it's the informal mentoring relationships that have a major impact on one's life. Both Drs. Patrick Finan and Sharon Kozachik filled that role. From day one they became informal mentors, offering both academic and career advice. They also became valuable collaborators in the process.

The current and future Drs. Jiayun Xu, Kyounghae Kim, Jocelyn Anderson, Yvonne Commodore-Mensah, and Grace Ho. We started as colleagues, but end as friends. As my dissertation support group, they gave the best advice, support, forum to write and speak my mind, and encouragement throughout this process.

Finally, these acknowledgments would not be complete without thanking my family, Mom (Kathy), aunt Susie, uncle Dan, grandma and grandpa Moscou, and my fiancé (Shomari). You set the standard and told me to "stop worrying…things will work out" along the way. I definitely could not have started or finished without your love and support.

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CHAPTER ONE: INTRODUCTION

Background and Significance

Sickle cell disease (SCD) is a group of inherited autosomal recessive hemolytic disorders. Approximately 7% of the world's population carries the genetic sickle hemoglobin mutation (HbS; McCavit, 2012). There are several genetic variants of SCD, which arise from inheritance of a copy of the HbS (sickle) gene from one or both parents. The most common genetic variants are HbSS (the most severe form), HbSC, and HbS/β^0-thalassemia (Ashley-Koch, Yang, & Olney, 2000; National Heart Lung and Blood Institute, 2012). Individuals who inherit one HbS gene and a normal hemoglobin gene (HbA) are considered carriers of the sickle cell trait and generally do not have signs or symptoms of the disease (National Heart Lung and Blood Institute, 2012). In the United States, approximately 100,000 Americans have SCD (Hassell, 2010) and it estimated that 1 in 500 African-Americans and 1 in 36,000 Hispanic-Americans are born with the disease each year (National Heart Lung and Blood Institute, 2012). Overall, SCD affects millions, but is common among individuals with ancestors from the sub-Saharan Africa and Middle East/India regions where malaria is prevalent (McCavit, 2012; National Heart Lung and Blood Institute, 2012).

Morbidity and mortality associated with SCD occurs when red blood cells with abnormal hemoglobin depolymerize and form a "sickle" shape (Ashley-Koch et al., 2000). Sickle-shaped red blood cells become inflexible and stick together, which interferes with their passage through the blood vessels. Blood vessels become blocked slowing transport of blood, nutrients, and oxygen to the tissues and organs supplied by the blocked blood vessel (Ashley-Koch et al., 2000; National Heart Lung and Blood

Institute, 2012). Any tissue or organ may be affected and prolonged blockage can lead to tissue necrosis, organ failure, or death. Despite the potentially deadly consequences of SCD, individuals with the disease are living longer because of advances in preventive care services over the last 40^{+} years. It is now expected that individuals with SCD can live past the 5^{th} decade of life (Hassell, 2010). With a longer life expectancy, Health-Related Quality of Life (HR-QOL) across the lifespan has become a larger priority for individuals with SCD (National Heart Lung and Blood Institute, 2002; Treadwell, Hassell, Levine, & Keller, 2014). We know from the literature that among individuals with SCD, the experience of symptoms, when distressing, is negatively associated with HR-QOL (Sogutlu, Levenson, McClish, Rosef, & Smith, 2011). As such, ameliorating or reducing the occurrence and distress is a quality of life priority.

While the hallmark symptom of SCD is a pain crisis (Niscola, Sorrentino, Scaramucci, de Fabritiis, & Cianciulli, 2009; Steinberg, 2011), there is growing evidence that sleep disturbances, specifically insomnia symptoms, are distressing for individuals with SCD. Sleep disturbance is a general term for a variety of subjective and objective sleep complaints (symptoms) associated with alterations in sleep/wake patterns (Cormier, 1990). Insomnia is a specific type of sleep disturbance and has been defined as both a set of symptoms and a sleep disorder in the medical and scientific literature. The broadest definition of insomnia (most often used in research) is a set of symptoms subjectively reported as difficulty initiating sleep, maintaining sleep, unintended early morning awakening, and/or non-restorative sleep with daytime consequences such as fatigue or cognitive impairment (Roth, 2007; Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). It is estimated that up to 30% of Americans suffer from one or more insomnia

symptoms (Schutte-Rodin et al., 2008). Stricter criteria define insomnia as a sleep disorder. Diagnosis of an insomnia disorder depends on the presence of those symptoms previously mentioned, in addition to persistence of these symptoms for one month or longer and occurring despite the opportunity to obtain adequate sleep (*American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, 2013). Application of stricter insomnia criteria lowers the prevalence of insomnia as a sleep disorder to 10% or less of the American population (Schutte-Rodin et al., 2008). Regardless of the definition applied, insomnia is a significant public health problem (Colten, Bruce M. Altevogt Editors, & Research, 2006; Schutte-Rodin et al., 2008) and is recognized as a comorbid condition in patients with chronic diseases (Katz, 1998; National Center on Sleep Disorders Research, 2003).

Growing evidence over the past 10 years suggests that 40-70% of individuals with SCD experience general sleep disturbances (Barker et al., 2012; Jacob et al., 2006; Sogutlu et al., 2011; Wallen et al., 2014). Insomnia symptoms, specifically difficulty falling asleep and staying asleep have also been reported (Daniel, Grant, Kothare, Dampier, & Barakat, 2010; Palermo & Kiska, 2005), but have not been systematically evaluated as a disorder or set of symptoms. Only one study to-date reported a 47% prevalence of insomnia symptoms among of the adults with SCD; however their estimates were based on a retrospective review of medical records, which may not be accurate due to the providers screening and/or documentation practices (Mann-Jiles, Thompson, & Lester, 2015).

Risk factors for general sleep disturbances have been investigated, primarily in children with SCD, however no studies to-date have confirmed their associated risk with

insomnia symptoms. Among these risk factors is depression (Palermo & Kiska, 2005), psychological stress (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007; Weisberg, Balf-Soran, Becker, Brown, & Sledge, 2013), hypoxemia secondary to obstructive adenotonsillar hypertrophy (Daniel et al., 2010; Long, Krishnamurthy, & Palermo, 2008; Rogers, Lewin, Winnie, & Geiger-Brown, 2010; Salles et al., 2009), and clinical pain (Beyer, Simmons, Woods, & Woods, 1999; E Jacob, 2001; Eufemia Jacob et al., 2006; Valrie, Gil, et al., 2007; Walco & Dampier, 1990).

Pain is a common risk factor of sleep disturbances among individuals with SCD with many studies showing that sleep is impaired when the individual experiences increased pain severity (Beyer et al., 1999; E Jacob, 2001; Eufemia Jacob et al., 2006; Valrie, Gil, et al., 2007; Walco & Dampier, 1990; Wallen et al., 2014). Although studies support the notion that pain impairs sleep, it is important to note that the sleep-pain relationship is likely bidirectional (Cole, Dubois, & Kosinski, 2007; Heffner, France, Trost, Ng, & Pigeon, 2011).

Depressive symptomatology is another likely risk factor of sleep disturbances in individuals with SCD. One recent study in adults with SCD found a high correlation between sleep disturbances and depressive symptoms ($r = 0.5$, $p < 0.001$); however they did not examine whether this association persisted after controlling for other patient characteristics that may confound this relationship (Wallen et al., 2014). In another study, Palermo & Kiska (2005) found that depressive symptoms explained 10% of the variance in sleep disturbances, however the sample was a group of adolescents with chronic pain conditions including SCD rather than SCD alone (Palermo & Kiska, 2005). While depression is a risk factor for the development of sleep disturbances, it is important to

note that this relationship is also likely bidirectional (Jansson-Fröjmark & Lindblom, 2008; Sivertsen et al., 2012).

To-date, only one study has quantitatively investigated psychological stress as a risk factor for sleep disturbances in patients with SCD. In this study, stress negatively correlated sleep disturbances (Valrie, Gil, et al., 2007). However in the qualitative literature, a participant stated "And I would be scared to go to sleep, because I would think I was going to die in my sleep" suggesting that psychological stress is also a risk factor for sleep disturbances among patients with SCD (Weisberg, Balf-Soran, Becker, Brown, & Sledge, 2013).

Finally hypoxemia during sleep is a risk factor, however this risk factor is most commonly associated with obstructive sleep apnea (OSA; Daniel et al., 2010; Long et al., 2008; Rogers et al., 2010; Salles et al., 2009) secondary to adenotonsillar hypertrophy (ATH; Salles et al., 2009). Adenotonsillar hypertrophy is an enlargement of adenoid tissue around the tonsils which is most common in children with the disease (Abou-Elhamd, 2012). It is unclear whether hypoxemia during sleep secondary to ATH persists into adulthood, especially among adults with SCD who have had their tonsils removed.

Regardless of the risk factor, obtaining quality sleep is important because sleep is restorative and untreated sleep disturbances, and specifically insomnia symptoms are associated with a number of negative psychosocial and physiological outcomes (National Center on Sleep Disorders Research, 2003). Among those outcomes are increased morbidity and mortality (National Center on Sleep Disorders Research, 2003; Tanabe et al., 2010), worsening pain (Buenaver et al., 2012; Tanabe et al., 2010), increased fatigue (Bower et al., 2011; Illi et al., 2012), decreased productivity at school and work (Colten

et al., 2006; Daley et al., 2009; Roth, 2007), increased use of unscheduled health care services (Daley et al., 2009; Foley, Sarsour, Kalsekar, & Walsh, 2010), and decreased quality of life (Colten et al., 2006; Long et al., 2008; Palermo & Kiska, 2005).

Given the potentially high prevalence of insomnia symptoms noted among adults with SCD and limited published studies of insomnia symptoms in this population, a methodologically rigorous and systematic examination of the prevalence and potential risk factors (or predictors) should be undertaken to understand the scope and complexity of this sleep abnormality. Clinical guidelines currently recommend that systematic investigations of insomnia include a history of sleep complaints with a history of other factors known to precipitate and perpetuate insomnia (i.e. medical and psychiatric co-morbidities and substance abuse; Schutte-Rodin et al., 2008). In some instances, objective measures of sleep (e.g. polysomnography or actigraphy) may also be used to assess insomnia severity, although these tools are not routinely recommended. According to clinical guidelines for the assessment and diagnosis of insomnia, polysomnography is not routinely recommended for evaluation of insomnia unless there is suspicion of comorbid obstructive sleep apnea (Schutte-Rodin et al., 2008). In addition, there is not enough evidence to recommend routine use of actigraphy as a diagnostic tool in populations other than healthy adults (Aetna, 2012; Morgenthaler et al., 2007; Schutte-Rodin et al., 2008; Van de Water, Holmes, & Hurley, 2011). Alternatives to PSG and actigraphy, which have shown convergent validity with specific quantitative measures of PSG include sleep diaries, symptom checklists, and self-report surveys (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Cole et al., 2007; Schutte-Rodin et al., 2008). The Insomnia Severity Index is one of a few self-report surveys that were specifically

designed to screen and evaluate treatment of insomnia symptoms rather than general sleep disturbances (Bastien, Vallières, & Morin, 2001). Other subjective measures such as sleep diaries can also be useful as they provide a day-to-day assessment of insomnia symptoms, risk factors, and outcomes, that cannot be examined with one-time self-report surveys alone (Buysse et al., 2006; Haythornthwaite, Hegel, & Kerns, 1991).

Study Purpose

This purpose of this study is add to existing research on the symptom experience and health-related quality of life in patients with chronic diseases by examining sleep disturbances and insomnia symptoms among adults with SCD. This study specifically 1) identifies the prevalence and potential risk factors (or predictors) of insomnia symptoms and 2) examines the relationship between insomnia symptoms, clinical pain, quality of life, and acute care utilization, which are potential negative outcomes of the insomnia symptom experience.

Specific Aims

Using a sample of African-American adults who are diagnosed with SCD and reside on the East Coast, the specific aims of this study are to:

Aim 1. Identify the situational, psychological, and physiologic factors that are associated with insomnia symptoms.

$H_{1.1}$: Situational factors are associated with insomnia symptom severity.

Lower educational attainment will be associated with increased insomnia symptom severity as compared to higher educational attainment. Also, individuals who are unemployed or not working because of a disability will

report higher insomnia symptom severity than individuals who are employed or not disabled.

$H_{1.2}$: Psychological factors are associated with insomnia symptom severity. *Increased life stressors and increased depressive symptomatology will be associated with increased insomnia symptom severity.*

$H_{1.3}$: Physiologic factors are associated with insomnia symptom severity. *Increased age, pain severity, and number of co-morbidities will be associated with greater insomnia symptom severity. Also, females and individuals with HbSS SCD hemoglobinopathy will report higher insomnia symptom severity compared to males and individuals with other SCD hemoglobinopathies.*

Aim 2. Examine the relationship between sleep duration, sleep onset latency, sleep fragmentation and clinical pain severity.

$H_{2.1}$: Decreased sleep duration, increased sleep onset latency, and increased sleep fragmentation will be associated with increased clinical pain.

$H_{2.2}$: The synergistic effect of decreased sleep duration and increased sleep fragmentation will be associated with the highest clinical pain severity.

Aim 3. Examine the relationship between insomnia symptom severity and perceived quality of life (EXPLORATORY).

$H_{3.1}$: Greater insomnia symptom severity will be associated with lower perceived quality of life.

$H_{3.2}$: Insomnia symptom severity will be an independent predictor of perceived quality of life after controlling for pain, depression, and socio-demographic characteristics that are associated with insomnia symptom severity.

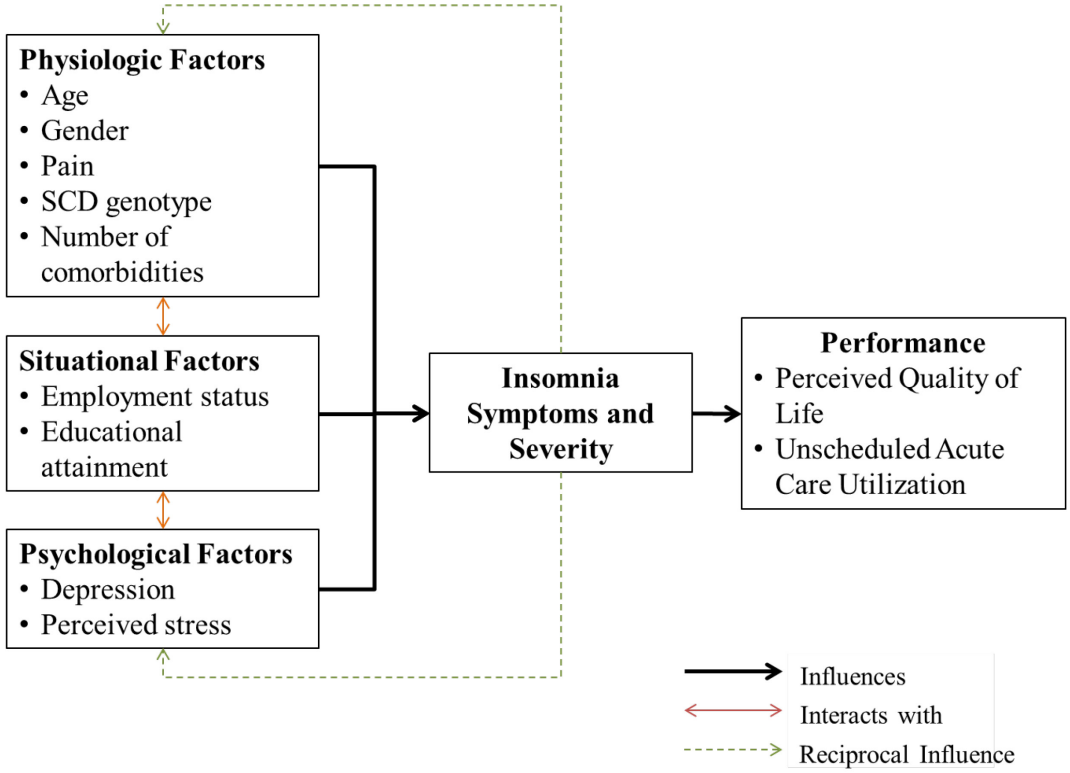
Aim 4. Examine the relationship between insomnia symptom severity and unscheduled acute care utilization (EXPLORATORY).

$H_{4.1}$: Greater insomnia severity will be associated with increased unscheduled acute care utilization.

$H_{4.2}$: Insomnia symptom severity will be an independent predictor of unscheduled acute care utilization after controlling for SCD genotype, pain, and socio-demographic characteristics that are associated with insomnia symptom severity.

Conceptual Framework

Figure 1.1. Adapted Theory of Unpleasant Symptoms Conceptual Framework



Adapted from: Lenz, E., Pugh, L., Milligan, R., Gift, A., and Suppe, F. (1997). The Middle-Range Theory of Unpleasant Symptoms: An Update. Advances in Nursing Science. 19(3):14-27.

The theory of unpleasant symptoms (TOUS) guided the examination of predictors and outcomes of insomnia symptoms for this study (Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz, Suppe, Gift, Pugh, & Milligan, 1995). The TOUS is a complex and synergistic middle-range nursing theory. The TOUS posits there are physiologic, psychological, and situational factors, which influence an individual's predisposition towards the development of unpleasant symptoms (Lenz et al., 1997, 1995). Furthermore, an individual's symptom experience is unique and characterized by "*intensity*," "*quality*,"

"*distress*," and "*duration*." If the symptom is perceived as distressing and unpleasant, the individual's cognitive functioning, physical performance, and functional status may be affected (Lenz et al., 1997, 1995). A unique concept in the updated TOUS theory is the idea that symptoms may be experienced alone, in conjunction with other symptoms, or symptoms may precede each other (Lenz et al., 1997). Furthermore, there can and may be a reciprocal interaction between the symptom experience and each bio-psychosocial factor contributing to the development of such symptom (Lenz et al., 1997). The TOUS has been used in symptom research studies and is being used to examine insomnia symptoms, risk factors, and outcomes in this study. Figure 1.1 is an adapted TOUS conceptual framework, which graphically displays the relationships between insomnia symptoms, bio-psychosocial predictors, and outcomes that are examined in this study.

Dissertation Organization

This dissertation is organized into five chapters. Chapter One is the introduction and provided the background for this study. Key concepts were defined, the study aims were described, and the TOUS conceptual framework used to ground this study and manuscripts was explained.

Chapter Two (Manuscript One) uses data from the Improving Patient Outcomes with Respect and Trust (IMPORT) study to psychometrically evaluate the reliability and validity of the Insomnia Severity Index (ISI) in adults with SCD.

Chapter Three (Manuscript Two) uses data from the IMPORT study to examine the prevalence of insomnia symptoms. Additionally, potential risk factors (or predictors) are examined to understand the scope and complexity of this sleep abnormality among adult patients with SCD.

Chapter Four (Manuscript Three) uses data from the Clinical Implications of Pain Phenotypes in Sickle Cell Disease Study to examine the relationship between insomnia symptoms, as measured through daily electronic diaries, and SCD clinical pain. This manuscript specifically examines the influence of quantifiable parameters of daily sleep continuity, primarily sleep duration and sleep fragmentation, on daily pain in adults with SCD.

Chapter Five summarizes the salient findings from manuscripts one, two, and three and presents preliminary findings from two additional exploratory aims that examine the association between insomnia symptom severity and perceived health status and healthcare utilization. The implications of all findings for research and practice are also discussed in this chapter.

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CHAPTER TWO: MANUSCRIPT ONE

Psychometric Validation of the Insomnia Severity Index in Adults with Sickle Cell Disease

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This manuscript is intended for submission to the

Journal of Healthcare for the Poor and Underserved

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Abstract: **Background.** The Insomnia Severity Index (ISI) is an instrument to evaluate insomnia symptoms. The psychometric properties of the ISI haven't been established in adults with Sickle Cell Disease (SCD). **Objective.** To evaluate the reliability and validity of the ISI among a sample of adults with SCD. **Methods.** Participants were ≥ 18 years of age and had SCD. Analysis included psychometric evaluation with factor analyses. **Results.** Our 263 participants had a mean age of 35.6 years and were 54.8% female. Almost 41% were classified as clinical insomnia cases (ISI ≥14) using the traditional scoring approach. Factor analysis identified a two-factor structure consisting of factors "Insomnia Symptoms" and "Insomnia Impact." Reliability for both factor-scales was good. Both factor-scales correlated with pain severity and depressive symptomatology (r = 0.38 to 0.66, $p<.01$). **Conclusion.** The ISI demonstrated construct validity and reliability for evaluating insomnia symptomatology among adults with SCD.

Keywords: Anemia, Sickle Cell; Factor Analysis, Statistical; Questionnaires; Validation Studies [Publication Type]

Introduction

Sickle Cell Disease (SCD) is a group of autosomal recessive hemolytic genetic disorders (Ashley-Koch, Yang, & Olney, 2000). In the United States, approximately 100,000 Americans are estimated to have Sickle Cell Disease (National Heart Lung and Blood Institute, 2012). Individuals with SCD experience a variety of disorder-related symptoms including sleep disturbances where prevalence estimates of up to 70% have been reported (Barker et al., 2012; Sogutlu, Levenson, McClish, Rosef, & Smith, 2011; Wallen et al., 2014). Two common sleep disturbances are difficulty initiating sleep (Daniel, Grant, Kothare, Dampier, & Barakat, 2010; Palermo & Kiska, 2005) and maintaining sleep (Daniel et al., 2010), which are key symptoms of insomnia when they cause distress and/or impact daytime function (*American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, 2013). The etiology of sleep disturbances has been attributed to nocturnal hypoxemia secondary to obstructive sleep apnea (Daniel et al., 2010), depression (Barker et al., 2012; Wallen et al., 2014), and pain (Barker et al., 2012; Valrie, Gil, Redding-Lallinger, & Daeschner, 2007; Wallen et al., 2014).

Polysomnography (PSG) is the gold standard for objectively measuring sleep and diagnosing sleep disorders. However, PSGs are not currently indicated for routine diagnosis of insomnia in the absence of risk factors. The gold standard for diagnosing insomnia is a clinician interview (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008), however interviews are time-consuming and require the clinician to have in-depth knowledge about insomnia (Morin, Belleville, Bélanger, & Ivers, 2011). Thus, self-report remains the primary approach to screening and quantifying insomnia severity (Morin et

al., 2011). In routine clinical practice settings, brief screening instruments which have been shown to be sensitive to interventions, such as the Insomnia Severity Index (ISI), can be extremely useful.

The ISI is a 7-item self-report instrument that measures perceived insomnia symptoms, concern or distress, and interference with daily functioning over the past two weeks (Bastien, Vallières, & Morin, 2001; Morin et al., 2011). Concurrent and convergent validity with other measures of insomnia symptoms including PSG parameters, sleep diaries, and clinician interviews have been established for this instrument (Bastien et al., 2001; Morin et al., 2011). The ISI, which was originally validated in a group of patients with insomnia (mean age of 65 years; Bastien et al., 2001) has since been validated in adults without sleep disturbances (Gagnon, Bélanger, Ivers, & Morin, 2013; Morin et al., 2011), adolescents (Chung, Kan, & Yeung, 2011), individuals with cancer (Savard, Savard, Simard, & Ivers, 2005), and translated into several languages (Cho, Song, & Morinc, 2014; Chung et al., 2011; Fernandez-Mendoza et al., 2012; Sadeghniiat-Haghighi, Montazeri, Khajeh-Mehrizi, Nedjat, & Aminian, 2013; Yu, 2010). Overall, the ISI has been widely used to evaluate insomnia symptom severity and treatment response to both sedative hypnotics and behavioral treatments for insomnia (Bastien et al., 2001).

To our knowledge, although widely used in research and practice, the ISI has only been validated in one chronic disease population (i.e. cancer) and has not been validated to assess subjective sleep complaints in individuals with SCD, a unique chronic pain population. Furthermore, both two- and three-factor solutions for the ISI have been proposed using factor analytic approaches, yet the ISI has been predominantly used as a

one-dimensional instrument in clinical and research applications. Thus, before recommending routine use of the ISI to evaluate insomnia symptoms in patients with SCD, the psychometric properties of the ISI among this patient population should be evaluated.

Methods

Participants and Setting. Participants are a subsample from the Improving Patient Outcomes with Respect and Trust (IMPORT) study. IMPORT is a federally funded, multi-site longitudinal observational study designed to evaluate SCD patients' experiences with respect and trust in routine healthcare environments and its effect on adherence to therapy, appropriateness of care, and health outcomes.

IMPORT participants were a convenience sample of individuals recruited from SCD clinics at Johns Hopkins Hospital (Baltimore, MD) and Howard University Hospital (Washington, DC). A total of 291 individuals who were ≥16 years of age, had a self-reported diagnosis of a SCD hemoglobinopathy, and provided informed consent were included in the parent study. For this analysis, the 263 participants who were ≥18 years of age at enrollment and provided complete data on the ISI during the baseline visit were included. IMPORT was approved by the institutional review boards at the Johns Hopkins University School of Medicine and Howard University School of Medicine.

Measures. *Insomnia Severity Index (ISI).* The ISI measures perceived insomnia symptomatology (Bastien et al., 2001). Each item is scored on a 5-point likert scale from zero ("none" or "not at all") to four ("extremely"). The traditional scoring approach is to sum scores across all items. Higher total scores (range zero to 28) indicate greater insomnia symptom severity (Bastien et al., 2001). Comparison between ISI scores, PSG

parameters, and clinician interviews has helped to identify clinical cut-off scores for identifying cases of insomnia. Estimates vary across studies, however ISI scores of 10 or greater appear to be optimal for identifying clinically significant insomnia symptoms in non-sleep clinic samples (Gagnon et al., 2013; Morin et al., 2011; Savard et al., 2005), while scores of 14 or greater identify clinical insomnia cases with a high degree of accuracy (Gagnon et al., 2013; Morin et al., 2011; Savard et al., 2005). Overall, the ISI has demonstrated good reliability across population groups (Cronbach's alpha 0.74-0.91; Bastien et al., 2001; Chung et al., 2011; Fernandez-Mendoza et al., 2012; Gagnon et al., 2013; Morin et al., 2011; Sadeghniiat-Haghighi et al., 2013; Savard et al., 2005; Yu, 2010).

Multiple studies have explored the factor structure of the ISI. The developers of the instrument reported a three-factor structure (i.e. "severity of symptoms," "satisfaction with sleep," and "distress associated with sleep difficulty") among a sample of participants with insomnia (Bastien et al., 2001). This factor structure was replicated by the developers of the Spanish version of the ISI (Fernandez-Mendoza et al., 2012). In four additional studies, however, a two-factor structure was found (i.e. "severity of symptoms" and "impact of sleep difficulties") among samples of adults with breast and prostate cancer (Savard et al., 2005), Persian sleep clinic patients (Sadeghniiat-Haghighi et al., 2013), Chinese school-based adolescents (Chung et al., 2011), and older adults (Yu, 2010). Despite the aforementioned factor solutions, clinical evaluations and research and have predominately used the ISI as a one-dimensional construct.

Center for Epidemiology Studies in Depression (CESD-10). The CESD-10 measures the degree of depressive symptomatology experienced over the previous week

(Andresen, Malmgren, Carter, & Patrick, 1994). Each item is scored on a 4-point likert scale from zero ("Rarely or None of the time") to three ("Most or all of the time"). In general, higher total scores across items indicate a greater degree of depressive symptomatology (Andresen et al., 1994). The CESD-10 is a valid and reliable measurement tool with good internal consistency (Cronbach's alpha = 0.79) among African American adults with SCD (Laurence, George, & Woods, 2006).

Brief Pain Inventory (BPI). The BPI measures clinical pain in patients with acute and chronic pain conditions (Cleeland, 2009). The BPI measures two distinct constructs of the pain experience, perceived pain severity (four items) and impact of pain on daily functioning (seven items). For our analysis, items from the pain severity sub-scale were used. The pain severity sub-scale measures "worst," "least," "average," and "current" pain severity experienced within the past 24 hours on a numerical rating scale (range zero ("no pain") to ten ("as bad as you can imagine")). A BPI severity composite score (mean severity score) was calculated, with higher scores indicating greater pain severity (Cleeland, 2009). The BPI has been psychometrically and linguistically validated and is a reliable measure of clinical pain (Cronbach's alpha for the BPI pain severity sub-scale 0.80 to 0.87; Cleeland, 2009)

Demographic Characteristics. Demographic information including: age, gender, education, and employment status were assessed with a self-report demographic questionnaire.

Analysis. All statistical analyses were performed using Stata version 13.0 (StataCorp, 2013). Descriptive summary statistics were used to examine demographic and clinical characteristics of the sample. Insomnia symptom characteristics were also initially

described using the traditional summary (one-factor) score in order to compare our sample's scores with published scores from other non-SCD populations, which have used the traditional scoring approach.

We used two common methods to assess the ability of the ISI to measure the construct "insomnia symptomatology" and underlying dimensions of this construct. We conducted a reliability assessment using measures of internal consistency. We assessed factorial and construct validity using factor analysis and by examining the correlation between the ISI and theoretically-related constructs. As a general rule, when conducting factor analyses at least 10 participants per item or greater than 200 participants is recommended (Comrey & Lee, 1992; Nunnally, 1978). Therefore, our sample size of 263 participants provided a sufficiently large sample to perform the subsequent analyses.

To explore the factor structure of the ISI, we used exploratory factor analysis (EFA) with maximum likelihood estimation. We examined the Determinant of the correlation matrix, Bartlett's test of sphericity and the Kaiser-Meyer Olkin (KMO) test to assess the adequacy of the correlation matrix for conducting factor analyses. Factors were extracted and refined using principal axis factoring with oblique promax rotation since we hypothesized that multiple factors would be correlated. The number of factors retained was determined by the eigenvalue > 1.0 guideline, examination of Akaike's Information Criterion (AIC) values, and interpretability of the factors.

After identifying the factor structure, we created composite factor-scales for each identified factor by calculating mean scores across items that loaded >0.40 on each factor (Pett, Lackey, & Sullivan, 2003). Reliability and validity analyses were performed on the resulting factor-scales. To assess reliability, a Cronbach's alpha was calculated for each

factor-scale. Spearman's correlation was used to examine construct validity between each subscale and theoretically-related constructs (i.e. clinical pain and depressive symptomatology).

Results

Descriptive characteristics of the sample are displayed in Table 2.1. Participants ranged from 18 to 70 years of age (mean age 35.6 years). Most of the sample was female (54.8%), had a high school or less education (61.2%), and was disabled (43.0%). Scores on the BPI severity scale ranged from the lowest possible to the highest possible for and almost the highest for the CESD-10. Using the traditional scoring approach, approximately 40.7% of the sample would be classified as a clinical insomnia case (ISI summary score of 14 or greater). This estimate is well above the estimated 10% prevalence of chronic clinical insomnia cases nationally (Roth, 2007), but similar to the prevalence of general sleep complaints reported by individuals with SCD (Barker et al., 2012; Sogutlu et al., 2011).

Factor Analysis. Examination of the correlation matrix indicated that all items on the ISI significantly correlated with other items in the matrix (range 0.44 - 0.75). The Determinant of the Correlation matrix was 0.013 and the Bartlett's test of sphericity was significant ($\chi^2 = 1129.1$, $p < .05$), which also suggested the suitability of the correlation matrix to conduct factor analyses. Finally, the KMO statistic was 0.908, which suggested a high degree of shared variance and adequacy for factor analysis.

Initially, we examined results for a one-factor model of the ISI. The one-factor solution explained 91.2% of the variance among ISI items (eigenvalue = 4.2). We then tested a two-factor model using oblique rotation. This model identified two distinct

factors we named "Insomnia Symptoms" and "Insomnia Impact" (see Table 2.2.). Each factor accounted for approximately one half of the total variance (50.9% and 49.1% of variance, respectively). The factor "Insomnia Symptoms" was composed of the first three items of the ISI (i.e. "Difficulty falling asleep," "Difficulty staying asleep," and "Problem waking up too early"), while "Insomnia Impact" was composed of the last four items (i.e. "Satisfaction with current sleep problem," "Interference with daily functioning," "Noticeability of sleeping problem," and "Worry about current sleep problem"). Examination of AIC values for the one and two-factor models suggested that the two-factor model was the best fit (AIC = 34.9, $df = 13$). The mean composite score for the "Insomnia Symptoms" factor-scale was 1.50 (range 0.0 to 4.0), and the mean score of the "Insomnia Impact" factor-scale was 1.66 (range 0.0 to 4.0). Table 2.3 shows a significant correlation between the two factor-scales ($r = 0.77$, $p < .001$).

Internal Consistency Reliability. Reliability estimates for the two factor-scales are presented in parentheses on the diagonal in Table 2.4. Reliability statistics demonstrated good internal consistency among items in each factor-scale (Cronbach's alpha = 0.85 and 0.87, respectively).

Construct Validity. Correlations between ISI subscales and theoretically-related constructs were also examined. Results revealed "Insomnia Symptoms" significantly correlated with pain severity ($r = 0.41$, $p<.01$) and depressive symptomatology ($r = 0.60$, $p<.01$). Furthermore, "Insomnia Impact" also significantly correlated with pain severity ($r = 0.38$, $p<.01$) and depressive symptomatology ($r = 0.66$, $p<.01$).

Discussion

Results of this analysis suggest the ISI has good internal consistency and construct validity among our sample of respondents with SCD. We suggest, then, that the ISI is a valid and reliable instrument for evaluating insomnia symptoms in research and clinical practice involving patients with SCD.

Using EFA, we identified two distinct factors, "Insomnia Symptoms" and "Insomnia Impact," among the 7-items of the ISI. Similar to other validation studies, we found the first three items (i.e. "Difficulty falling asleep," "Difficulty staying asleep," and "Problem waking up too early") and the last three items (i.e. "Interference with daily functioning," "Noticeability of sleeping problem," and "Worry about current sleep problem") clustered together to represent two different dimensions of insomnia symptomatology (Bastien et al., 2001; Chung et al., 2011; Fernandez-Mendoza et al., 2012; Sadeghniiat-Haghighi et al., 2013; Savard et al., 2005; Yu, 2010). However, our results differ slightly from most studies with two-factor solutions for the ISI, notably Savard et al. (2005), Sadeghniiat-Haghighi et al. (2013), and Yu (2010). Different from those studies, we found that the item "Satisfaction with current sleep problem" uniquely clustered with other items that comprised "Impact of insomnia symptoms" rather than "Insomnia symptoms." Differences in factor loadings between the present analysis, Savard et al. (2005), Sadeghniiat-Haghighi et al. (2013), and Yu (2010), on that item may be explained by their use of orthogonal factor rotation as opposed to our use of oblique factor rotation under our assumption of correlated factors. Nevertheless, it should be noted that Sadeghniiat-Haghighi et al. (2013) found "Satisfaction with current sleep problem" loaded only slightly higher on "Insomnia symptoms" versus "Insomnia impact" (0.57 and 0.52, respectively) using orthogonal factor rotation. Furthermore, Chung et al.

(2011) also used orthogonal factor rotation and obtained the same two-factor solution as found in our analysis. We believe that "Satisfaction with sleep pattern" conceptually and empirically fits better with "Insomnia impact," however, future studies using this instrument among adults with SCD or other chronic disease and chronic pain populations should be undertaken to confirm the results found in our analysis.

The reliability and construct validity between ISI subscales and theoretically-related constructs found in our study further supports the use of the ISI in adults with SCD. We found the reliability of each subscale was good (Cronbach's alpha = 0.85 and 0.87) and the subscales correlated significantly, and in the expected direction, with measures of clinical pain and depressive symptomatology (r = 0.38 to 0.66, $p<.01$), with the strongest associations found between depressive symptomatology and both ISI subscales.

Our analysis has potential limitations. First, while our sample of 263 participants is within the recommended sample size required for exploratory factor analyses, a larger sample size (>500 participants) would have enhanced the precision of our estimates (Comrey & Lee, 1992). Second, we investigated the reliability and validity of the ISI in a sample of adults with SCD for whom a confirmed diagnosis of insomnia had not been established. Our results cannot be used to determine the accuracy of the ISI for identifying individuals at risk for clinically diagnosed insomnia as well as whether individuals with SCD and clinically diagnosed insomnia would respond differently than individuals with SCD and without clinically diagnosed insomnia. Third, the ISI was the only instrument used to evaluate insomnia symptoms therefore we were unable to establish concurrent validity between the ISI and other measures of insomnia

symptomatology. Finally, the present analysis is a cross-sectional investigation of the validity and reliability of the ISI therefore, we are unable to determine the stability over time of the ISI to measure insomnia symptomatology in this population.

Despite these limitations, our results suggest that the ISI is a valid and reliable instrument for evaluating self-reported insomnia symptomatology in adults with SCD. Furthermore, the ISI can be used to measure at least two dimensions of self-reported insomnia symptomatology, “Insomnia symptoms” and “Insomnia impact” in this population. Therefore, future studies should evaluate both ISI factor-scales as individual predictors or outcomes within the context of multivariate or multivariable regression analyses, which to our knowledge has not been investigated to-date.

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Table 2.1. Descriptive characteristics of the study participants (N=263)

Characteristic	*n* (%)
Age, years, Mean (SD)	35.6 (11.8)
Female	144 (54.8)
Education Level	
High School or less	161 (61.2)
Some College	44 (16.7)
College Graduate	54 (20.5)
Refused to Answer	4 (1.5)
Employment Status	
Working	94 (35.7)
Not Working	36 (13.7)
Disabled	113 (43.0)
Retired	9 (3.4)
Other	11 (4.2)
BPI Severity Score, median (range)	4 (0-10)
CESD-10 Score, median (range)	8 (0-29)

Table 2.2. ISI rotated two-factor pattern matrix: principal axis factoring with oblique promax rotation

	Factors Loadings	
	I	II
ISI Items by Factor		
I. Insomnia Symptoms		
1. Difficulty falling asleep	**0.53**	0.33
2. Difficulty staying asleep	**0.93**	0.04
3. Problem waking up to early	**0.67**	0.06
II. Insomnia Impact		
4. Satisfaction with current sleep pattern	0.29	**0.47**
5. Interference with daily functioning	0.07	**0.81**
6. Noticeability of sleep problem	0.01	**0.79**
7. Worry about current sleep problem	0.23	**0.64**

Table 2.3. Factor correlations and factor alpha coefficients for the composite sub-scales (N=263)

Factor	Mean Composite Score*	SD	Factors	
			I	II
I. Insomnia Symptoms (3 items)	1.50	1.07	(0.85)	
II. Insomnia Impact (4 items)	1.66	1.05	0.77†	(0.87)

Note: SD = Standard Deviation; *Range: 0.00 to 4.00, †$p < 0.01$

CHAPTER THREE: MANUSCRIPT TWO

Acute Pain and Depressive Symptoms: Independent Predictors of Insomnia Symptoms among Adults with Sickle Cell Disease

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Abstract

Background: No studies to-date have systematically investigated insomnia symptoms among adults with sickle cell disease (SCD). The purpose of this study was to 1) describe the prevalence of insomnia symptoms and 2) identify bio-psychosocial risk factors in community-dwelling adults with Sickle Cell Disease. **Methods:** Cross-sectional analysis of baseline data from 263 African-American adults with SCD (aged 18 years or older). Measures included the Insomnia Severity Index (ISI), the Center for Epidemiologic Studies in Depression scale, the Urban Life Stress Scale, the Brief Pain Inventory, and a chronic pain item. SCD genotype was extracted from the medical record. **Results:** A slight majority (55 %) of the sample reported clinically significant insomnia symptomatology (ISI ≥10), which suggests that insomnia symptoms are prevalent among community-dwelling African-American adults with SCD. While insomnia symptoms were associated with a number of bio-psychosocial characteristics, depressive symptoms and acute pain were the only independent predictors. **Conclusion:** Given the high number of participants reporting clinically significant insomnia symptoms, clinicians should screen for insomnia symptoms and explore individual and clinical interventions to promote better sleep among adults with SCD with an emphasis on treating pain and depression. In addition, current pain and depression interventions in this population could add insomnia measures and assess the effect of the intervention on insomnia symptomatology as a secondary outcome.

KEYWORDS (3-10): Insomnia, Sickle Cell Disease, Pain, Depression, Stress

Introduction

An estimated 90,000 to 100,000 people in the United States (US) are reported to have Sickle Cell Disease (SCD), a serious genetic disorder characterized by intermittent "sickling" of red blood cells (National Heart Lung and Blood Institute, 2012). Individuals with SCD may experience a number of serious consequences related to tissue and organ damage. Prior to the 1970s, individuals with SCD did not survive past the 2nd decade of life; however in the US, major advances in care, specifically comprehensive preventive care and awareness of early signs of illness, have improved the life expectancy of individuals with SCD to the seventh decade and beyond (National Heart Lung and Blood Institute, 2002, 2012). A shift to chronic disease management has brought an expressed desire by patients to focus on Health-Related Quality of Life (HR-QOL) across the lifespan (National Heart Lung and Blood Institute, 2002). The experience of symptoms, especially when distressing, has been negatively correlated with HR-QOL in adults with SCD (Sogutlu, Levenson, McClish, Rosef, & Smith, 2011).

While pain remains a major distressing symptom for patients with SCD (W R Smith et al., 2008), attention to other burdensome symptoms associated with decreased HR-QOL have increased in the literature during the past few years. Among these symptoms are sleep abnormalities, broadly described in the literature as "sleep disturbances." Sleep disturbance is a general term for a variety of subjective and objective sleep complaints associated with alterations in sleep/wake patterns and sleep disorders (Cormier, 1990). Sleep disturbances are common among patients with chronic disease (National Center on Sleep Disorders Research, 2003) and prevalence estimates of 40-70% (Barker et al., 2012; Jacob et al., 2006; Sogutlu et al., 2011; Wallen et al., 2014)

have been reported among children and adults with SCD. In children, specific sleep disturbances associated with the sleep disorder insomnia, namely difficulty falling asleep and staying asleep, have been identified using daily sleep diaries (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007). In addition, using retrospective chart review, one recent study found insomnia symptoms were documented for 47% of the adults with SCD (Mann-Jiles, Thompson, & Lester, 2015). Qualitative literature on sleep disturbances suggests that sleep disturbances have been reported as a distressing symptom (Panepinto, Torres, & Varni, 2012; Weisberg, Balf-Soran, Becker, Brown, & Sledge, 2013) and a quality of life priority for individuals with SCD (Treadwell, Hassell, Levine, & Keller, 2014). In addition, obtaining adequate sleep has been reported as a self-management strategy for preventing painful crises (Anderson & Asnani, 2013; Tanabe et al., 2010). Despite the prevalence and impact of sleep disturbances on quality of life among patients with SCD, there is a paucity of literature on factors that are associated with this symptom.

The present study was guided by the Theory of Unpleasant Symptoms (TOUS), which posits that physiologic, psychological, and situational factors influence the development and experience of symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz, Suppe, Gift, Pugh, & Milligan, 1995). Furthermore, an individual's symptom experience is unique and characterized by the symptoms "intensity," "quality," "distress," and "duration" (Lenz et al., 1997, 1995). Known predictors of sleep disturbances in patients with SCD include depression (Palermo & Kiska, 2005; Wallen et al., 2014) and pain (Valrie, Gil, et al., 2007; Wallen et al., 2014). Two other potential predictors, identified through studies in patients with SCD and other chronic diseases, are psychological stress and disease severity. In a qualitative study by Weisberg et al (2013),

a participant with SCD was quoted as saying "And I would be scared to go to sleep, because I would think I was going to die in my sleep" suggesting sleep disturbances may arise from stress, fear, and worry about the disease (Weisberg et al., 2013). In addition, across studies disease severity and disease activity are consistently identified as risk factors for sleep problems among chronic disease populations (Chandrasekhara, Jayachandran, Rajasekhar, Thomas, & Narsimulu, 2009; Frech et al., 2011; Martínez De Lapiscina, Aguirre, Blanco, & Pascual, 2012).

While a few studies have investigated sleep disturbances in adults with SCD (Sogutlu et al., 2011; Wallen et al., 2014), no studies to-date have systematically investigated insomnia symptoms in this population. Given sleep disturbances, specifically disturbances associated with insomnia, have been identified in individuals with SCD, examining the prevalence of insomnia symptoms and exploring potential risk factors (or predictors) should be undertaken to understand the scope and complexity of this sleep abnormality among adult patients with SCD. Therefore, the purposes of this study were to 1) describe the prevalence of insomnia symptoms and 2) identify biological and psychosocial predictors of the development and severity of insomnia symptoms among community-dwelling adults with Sickle Cell Disease.

Methods

Participants

This study is a cross-sectional analysis of baseline data provided by 263 African-American adults with SCD (aged 18 years or older) enrolled in the Improving Patients Outcomes with Respect and Trust (IMPORT) study. The IMPORT study was a prospective cohort study, which examined the experiences of care received by

adolescents and adults with SCD (age 15 years or older). Participants were conveniently recruited from SCD outpatient clinics in the Mid-Atlantic region. Individuals were eligible to participate if they were 1) 15 years or older, 2) had HbSS, HbSC, Hb SS/β^0-thalassemia, or Hb SS/β^+-thalassemia sickle hemoglobinopathies, and 3) no plan to move within three years of enrolling in the study. A total of 292 participants provided informed consent and were enrolled in the parent study between May 2010 and December 2011.

All study procedures were approved by Institutional Review Boards at both study sites. At baseline participants completed a battery of comprehensive validated questionnaires used to assess self-reported demographic, health-related, and psychosocial data. All self-report baseline data were collected using an audio computer-assisted self-interview (ACASI) system. In addition to baseline questionnaires, a trained research assistant extracted clinical health data from the participant's medical record.

Measures

Insomnia symptoms include difficulty initiating and/or maintaining sleep, unintended early morning awakening, and non-restorative sleep with daytime consequences (Roth, 2007; Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). We used the *Insomnia Severity Index (ISI)* to measure perceived severity of insomnia symptoms, concern or distress, and interference with daily functioning experienced during the past two weeks (Bastien, Vallières, & Morin, 2001; Morin, Belleville, Bélanger, & Ivers, 2011). Each item on the 7-item ISI is scored on a 5-point Likert scale from 0 ("not at all") to 4 ("extremely"). Overall, higher total scores (range zero to 28) indicate increased presence and severity of insomnia symptoms. Scores of 10 or higher can be used to identify clinically significant insomnia symptoms and scores over 14

identify clinical insomnia cases with a high degree of accuracy (Gagnon, Bélanger, Ivers, & Morin, 2013; Morin et al., 2011; Savard, Savard, Simard, & Ivers, 2005). Overall, we found the ISI had good internal consistency among participants in our sample (Cronbach's alpha was 0.91).

Baseline socioeconomic and demographic characteristics were included in this study as potential predictors of insomnia symptomatology. Socioeconomic and demographic characteristics included age, sex, educational attainment, and employment status were self-reported by participants.

Depressive symptomatology was a psychological predictor in this study. The 10-item *Center for Epidemiologic Studies in Depression (CESD)* scale was used to measure depressive symptomatology. Item response choices, on a 4-point Likert scale, range from 0 ("Rarely or none of the time") to 3 ("Most or all of the time) with a time frame of the past week. On the CESD-10, a summary score across items that can range from zero to 30 is calculated. Participants who score 10 or higher may be at risk for clinical depression (Andresen, Malmgren, Carter, & Patrick, 1994). The CESD-10 is a valid measure of depressive symptoms among African-American adults with SCD (Laurence, George, & Woods, 2006) and had good internal consistency reliability among participants in our sample (Cronbach's alpha = 0.83).

Perceived stress was another psychosocial predictor in this study. Perceived stress was measured using the 21-item *Urban Life Stress Scale (ULSS)*. The ULSS scale measures the degree of daily psychological and emotional stress experienced by defined contextual community-level stressors (Sanders-Phillips & Harrell, n.d.). Each item is measured on a 5-point Likert scale from 0 ("no stress at all") to 4 ("extremely stressful").

Scores from each item are summed to produce a total score from zero to 84, where higher scores indicate greater perceived life stress (Sanders-Phillips & Harrell, n.d.; Jaffee et al., 2005). The Cronbach's alpha for the ULSS was 0.89 for our sample.

Pain has been identified as a consistent risk factor for insomnia symptoms, thus was included as a biological predictor in this study. Given individuals with SCD experience both acute and chronic SCD pain (Wally R Smith & Scherer, 2010), we included a measure of both in this study. A single item, "Do you have daily chronic pain?" with response options of "yes" or "no" was asked. This item was not bound by a specific timeframe therefore participants were free to interpret whether they experienced chronic SCD pain. This item has been used in several studies of SCD by the IMPORT research team. In a prior study, the IMPORT team demonstrated that this item performed as well as "the number of good days the participant experiences each week" (higher score equals a lower burden of pain during the week) and "self-reported pain on a good day" (higher score equals more severe pain on a good day) (Haywood et al., 2014), which are other items used to measure the burden of chronic pain in adults with SCD. Therefore, we selected this item as a valid measure of chronic SCD pain for the current study.

To measure acute pain, we used the *Brief Pain Inventory (BPI).* The BPI is an instrument used to measure two dimensions of pain, pain severity (4-items) and the degree to which pain interferes with daily functioning and feelings (7-items; Cleeland, 2009). The pain severity items (i.e. "worst," "least," "average," and "current" pain rating in the past 24 hours) were used to measure acute pain severity. The response options ranged from 0 ("no pain") to 10 ("as bad as you can imagine"). A composite pain severity

score is created from the four BPI severity items (range zero to 10). The Cronbach's alpha for the BPI-severity questions was 0.87 in this study sample.

In the absence of a SCD-specific disease severity index (Coelho et al., 2012), SCD genotype (an individual's inherited genetic information) has been used (Grant, Gil, Floyd, & Abrams, 2000; Wison Schaeffer et al., 1999) and was used in this study as a measure of disease severity. *SCD genotype* (HbSS, HbSC, HbS/β^0-Thalassemia, and HbS/β^+-Thalassemia) was extracted from the participant's medical chart by trained research assistants using a medical record extraction form at baseline. In general, individuals with the HbSS or HbS/β^0-Thalassemia genotypes have similar phenotypic expressions (observable traits) and are generally more severely affected than individuals with HbSC or HbS/β^+-Thalassemia. Due to similarities in their severity profile, SCD genotype can be further dichotomized by phenotype expression (HbSS or HbS/β^0-Thalassemia versus HbSC or HbS/β^+-Thalassemia) and was for the present analyses.

Statistical Analysis

Participant characteristics were described using means with standard deviations and frequencies with percentages where appropriate. A Cronbach's alpha was calculated for the ISI, CESD-10, and ULSS scales to evaluate the internal consistency reliability of these measures in our sample. Pearson's product correlations, t-tests, and one-way ANOVAs were used where appropriate to establish unadjusted relationships between insomnia symptom severity and potential bio-psychosocial predictors. As a final step, we used multiple linear regression analysis (backward-selection) to determine which bio-psychosocial characteristics were independently associated with insomnia symptom severity. All characteristics that were associated with insomnia symptom severity in the

bivariate analyses were included in the models. A probability of > 0.1 (two-tailed) was set as criteria for removal from the model and statistical significance was determined as a probability < 0.05 (two-tailed). All analyses were conducted using Stata 13 software (StataCorp, 2013).

We conducted an a priori power analysis to determine if our sample size was adequate for using multiple regression to identify a statistical model of predictors of insomnia symptoms. Power was set at the conventional 0.80 with statistical significance at 0.05. It was determined that a sample size of 263 participants provided adequate power for a regression model with a small to medium effect size (Cohen's $f^2 > 0$ .08).

Results

Participant Characteristics

Table 3.1. diplays characteristics for the 263 participants in this study. Seventy percent of the sample had SS or HbS/β^0-Thalassemia genotype. Educational attainment was low with 62.8% of the sample reporting less than a high school education. Further, a large proportion of the sample (42.6%) reported not working because of a disability. Although a slight majority of the sample reported experiencing chronic pain (56.6%), acute pain severity in the past 24 hours was low (3.8 out of 10). Approximately 41% of participants scored in the range for clinically significant depressive symptoms (CESD-10 ≥ 10; Andresen et al., 1994) and among this sample, insomnia symptom severity was high. A slight majority (55 %) of the sample reported clinically significant insomnia symptomatology (ISI ≥10), while 41% may have clinical insomnia (ISI ≥14; data not presented).

Characteristics Associated with Insomnia Symptom Severity

Age, sex, education, employment status, depressive symptomatology, perceived stress, pain, and disease severity were analyzed for their unadjusted association with insomnia symptom severity (**Table 3.2.**). Age, sex, and number of comorbidities were not associated with insomnia severity ($p > 0.05$). Overall, individuals with a college education or higher reported less insomnia severity than individuals who had less than a college education ($p = 0.03$). When comparing insomnia severity by employment status, there was only a significant difference in insomnia severity between individuals who were employed versus not working because of disability ($p = 0.03$). Individuals who were not working because of a disability reported greater insomnia severity than individuals who were not disabled ($p = 0.002$).

We found paradoxical findings between SCD genotype and insomnia severity. Individuals with genotype SS or HbS/β^0-Thalassemia reported significantly lower insomnia severity than individuals with SC or HbS/β^+-Thalassemia ($p = 0.02$). Finally, insomnia severity was associated with acute pain, chronic pain, perceived stress, and depressive symptoms. Individuals with chronic pain reported greater insomnia severity than individuals without chronic pain ($p < 0.001$). In addition, acute pain, depressive symptoms, and perceived stress were positively associated with insomnia severity ($p < 0.05$).

Independent Predictors of Insomnia Symptom Severity

A stepwise backward-selection linear regression model was tested to determine which characteristics were independently associated with insomnia symptom severity (**Table 3.3.**). Characteristics that were associated with insomnia symptom severity at the bivariate-level were included in the Model (i.e. education, disability status, SCD

genotype, pain (acute and chronic), perceived stress, and depression). Stepwise regression analysis revealed that only increased acute pain (β =0 .45, $p = 0.002$) and depressive symptoms ($\beta = 0.71$, $p < 0.01$) were independent statistical predictors of greater insomnia severity. Together, acute pain and depression accounted for 49% of the variability in insomnia symptom severity. In a post-hoc sensitivity analysis, we dichotomized our outcome according to the clinical cut-point for the insomnia severity index (ISI < 10 versus ISI ≥ 10). Using logistic regression, we found no difference in our results, which supported the validity of our findings.

Discussion

To our knowledge, this is one of the first studies to explore insomnia symptomatology and potential bio-psychosocial risk factors among community-dwelling adults with SCD. Overall, our results suggest that insomnia symptoms are commonly experienced by adults with SCD, with 55% of participants reporting insomnia severity scores above the clinical cut-off (ISI ≥ 10; Morin et al., 2011). The prevalence of insomnia symptoms in this study is higher than the 30% prevalence of insomnia symptoms found in the general population (Schutte-Rodin et al., 2008). Based on these findings, clinician's working with adult patients with SCD should routinely screen for insomnia symptoms and other signs of sleep disturbances.

We used the Theory of Unpleasant Symptoms (TOUS) and literature to guide our selection of bio-psychosocial factors believed to be independently associated with insomnia symptoms and severity in adults with SCD. Similar to other studies, we found that acute pain and depression were independent predictors of insomnia symptom severity (Buenaver et al., 2012; Chandrasekhara et al., 2009; Heffner, France, Trost, Ng,

& Pigeon, 2011; Huang & Lin, 2009; Palermo & Kiska, 2005; Palesh et al., 2007); however, among other potential risk factors, we found weak or non-significant associations.

We found that none of the socio-demographic characteristics were independently associated with insomnia symptom severity. It is possible these socioeconomic characteristics merely provide context rather than increased risk for the development of insomnia symptoms. Notably, although females are known to have a higher risk of developing insomnia symptoms (Roth, 2007), we found no significant differences in any characteristic between males and females in our study. This may suggest that at least in our sample, males and females were similar in their experiences with SCD.

We found perceived stress moderately and positively correlated with insomnia severity, however perceived stress was not an independent predictor after controlling for acute pain and depressive symptomatology. Another study that examined perceived stress and sleep disturbances in individuals with SCD found perceived stress was an independent risk factor (Valrie, Gil, et al., 2007). However this study did not control for depressive symptoms, which may explain differences between our findings.

Disease severity, as measured by SCD genotype, was also not an independent risk factor of insomnia symptom severity. Further, we found individuals with the SC or HbS/β^{+}-Thalassemia genotype reported more severe insomnia symptomatology than individuals with SS or HbS/β^{0}-Thalassemia which are considered the most severe genotypes. This finding is largely unsupported in the literature. However, anecdotally clinicians working with adults with SCD have noted that although higher morbidity is associated with individuals with SS or HbS/β^{0}-Thalassemia, the day-to-day experience is

similar for everyone. Overall, a small number of studies have investigated the relationship between symptoms including sleep disturbances and disease severity with mixed results. Among these studies, and in our study it was believed that disease severity would be positively associated with insomnia severity (Ameringer, Elswick, & Smith, 2014). It is possible that the measure of disease severity used in our study did not accurately capture disease severity. It is also possible that the association between disease severity and insomnia severity was weak and our study was underpowered to detect a predictive relationship.

Overall, we found that acute pain and depressive symptoms were the only independent risk factors for insomnia symptom development and severity. Depressive symptoms as a risk factor is supported by a cognitive model of insomnia in which worry, rumination, and stress lead to hyperarousal (Roth, 2007). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), insomnia is the most common sleep disturbance associated with a major depressive episode (*American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, 2013). In our study, approximately 40% of participants scored above the clinical cut-off (CESD-10 $\geq$ 10) for clinically relevant depression, which may also explain the high prevalence of insomnia symptoms found in our study.

Finally, numerous studies have found a relationship between pain and sleep disturbances in patients with chronic pain conditions including SCD (Valrie, Bromberg, Palermo, & Schanberg, 2013), therefore it is not surprising that this association was found for insomnia symptoms. However, different from previous studies, we found that acute pain was independently associated with insomnia symptoms, while chronic pain

was not. We hypothesize that, while pain and insomnia symptoms are common among patients with chronic pain conditions, acute pain superimposed on chronic pain is a more powerful risk factor than chronic pain alone.

Strength and Limitations

There are a few notable limitations in this study that cannot be ignored. First, data for this study come from self-report items, which may have been influenced by the participants emotional state at the time of reporting (Shiffman, 2000). In addition, in post-priori power analysis, we determined our sample size was likely too small to detect significant independent associations for bio-psychosocial characteristics that were very weakly associated with insomnia symptom severity. Finally, all potential explanatory variables of insomnia symptom severity were not investigated in this study. Other factors known to be associated with sleep disturbances in individuals with SCD such as personal habits, nocturnal hypoxemia secondary to obstructive sleep apnea (Bandla & Splaingard, 2004; Hollocks et al., 2012; Rogers, Lewin, Winnie, & Geiger-Brown, 2010) and inflammation (Bower et al., 2011; Heffner et al., 2011; Illi et al., 2012) may have explained more of the variance in insomnia severity, but were not collected as part of the parent study and, thus, could not be explored. Despite these limitations, we used an established theory to guide the selection of potential explanatory variables. Furthermore, although conveniently sampled, our study population is representative of the target population of persons diagnosed with Sickle Cell Disease, which enhances the generalizability of our results. We believe that the findings in this study can, at the least, be a spring board for clinical and research discussions about insomnia in adults with SCD.

Conclusion

Overall, this study found that clinically significant insomnia is prevalent among community-dwelling African-American adults with SCD. Furthermore, while insomnia symptoms may be associated with a number of bio-psychosocial factors, depression and acute pain may the only independent risk factors. Given the high number of participants reporting clinically significant insomnia symptoms, our exploration provides evidence that should encourage clinicians, including nurses, to proactively screen for insomnia symptoms and explore individual and clinical interventions to promote better sleep among adults with SCD with an emphasis on treating pain and depression. Future research should include quantitative (e.g. actigraphy) and self-report measures of sleep and model fluctuations in sleep patterns over time, which would provide the most holistic assessment of sleep. In addition, the exploration of a mediation model with stress and depression should also be explored in a larger sample given the adjusted regression analysis findings and hypotheses of the Theory of Unpleasant Symptoms. Finally, while support for randomized control trial interventions to promote sleep quality may be premature, current research on pain and depression interventions in this population could add insomnia measures and assess the effect of the intervention on insomnia symptomatology as a secondary outcome.

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Table 3.1. Participant characteristics[a]

	Total (N = 263) n (%)	Males (n = 119) n (%)	Females (n = 144) n (%)	p
Age, years*	35.6 (11.8)	34.9 (11.5)	36.2 (12.1)	0.38
Education				
High school or less	161 (62.2)	69 (59.5)	92 (64.3)	0.73
Some college education	44 (17.0)	21 (18.1)	23 (16.1)	
College Grad or greater	54 (20.9)	26 (22.4)	28 (19.6)	
Employment				
Working	94 (35.7)	45 (37.8)	49 (34.0)	0.66
Unemployed	36 (13.7)	15 (12.6)	21 (14.6)	
Disability	113 (43.0)	52 (43.7)	61 (42.4)	
Retired	9 (3.4)	2 (2.0)	7 (4.9)	
Other	11 (4.2)	5 (4.2)	6 (4.2)	
Genotype				
SS or HbS/β^0-Thalassemia	186 (70.7)	83 (69.8)	103 (71.5)	0.75
SC or HbS/β^+-Thalassemia	77 (29.3)	36 (30.3)	41 (28.5)	
Chronic Pain				
No	115 (43.4)	49 (41.2)	66 (46.2)	0.42
Yes	147 (56.1)	70 (58.8)	77 (53.9)	
BPI severity*	3.8 (2.5)	3.7 (2.6)	3.9 (2.4)	0.62
ULSS*	16.8 (12.0)	17.4 (12.4)	16.4 (11.7)	0.52

CESD-10*	8.9 (6.0)	9.1 (5.8)	8.8 (6.2)	0.68
ISI	11.1 (7.0)	11.0 (6.7)	11.3 (7.3)	0.73

Note: BPI = Brief Pain Inventory; CESD-10 = Center for Epidemiologic Studies in Depression; ISI = Insomnia Severity Index; ULSS = Urban Life Stress Scale

* Mean (SD)

[a] N = 263, smaller n's are related to missing data

Table 3.2. Association between Insomnia Symptom Severity and potential risk factors: pearson's correlation and student's t-test results

		t-test	Pearson's Correlation	
	M (SD)	**t(*df*)**	***r***	**p-value**
Age			0.06	0.34
Gender				
Males	10.97 (6.6)	-.34 (258.2)		0.073
Females	11.27 (7.3)			
Education				
Less than college	11.57 (6.9)	2.2 (81.3)		0.03
College or greater	9.19 (7.1)			
Disability Status				
Not Disabled	9.96 (7.0)	-3.1 (246.5)		0.002
Disabled	12.7 (6.7)			
Genotype				
SS or Beta (0) Thalassemia	10.44 (6.5)	-2.4 (123.7)		0.02
SC or Beta (+) Thalassemia	12.83 (7.7)			
Chronic Daily Pain				
No	8.29 (6.5)	-6.2 (245.3)		< 0.001
Yes	13.31 (6.6)			

No. Comorbidities	0.07	0.06
BPI Severity	0.41	< 0.001
ULSS	0.45	< 0.001
CESD-10	0.68	< 0.001

Note: BPI = Brief Pain Inventory; CESD-10 = Center for Epidemiologic Studies in Depression; ISI = Insomnia Severity Index; M = Mean; SD = Standard Deviation; ULSS = Urban Life Stress Scale

Table 3.3. Stepwise backward linear regression results for a model of independent predictors of insomnia symptomatology[a]

Variable	β (95% CI)	p-value
Constant	3.02 (1.73, 4.32)	0.002
Acute Pain (BPI)	0.45 (0.17, 0.73)	< 0.001
Depressive Symptoms (CESD-10)	0.71 (0.59, 0.82)	< 0.001
Disability Status		0.83
Chronic Pain		0.78
SCD Genotype		0.45
Educational Attainment		0.21
Stress (ULSS)		0.10

Note: BPI = Brief Pain Inventory; CESD-10 = Center for Epidemiologic Studies in Depression; SCD = Sickle Cell Disease; ULSS = Urban Life Stress Scale

[a] n = 217

CHAPTER FOUR: MANUSCRIPT THREE

The Effect of Sleep Continuity on Pain in Adults with Sickle Cell Disease

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This article was published in The Journal of Pain:

Moscou-Jackson, G., Finan, P., Campbell, C., Symth, J., Haythornthwaite, J. (Published Online 2015). The Moderating Effect of Sleep Fragmentation on the Association of Sleep Duration and Pain in Adults with Sickle Cell Disease. Journal of Pain. http://dx.doi.org/10.1016/j.jpain.2015.03.010.

Abstract: This analysis examined the influence of quantifiable parameters of daily sleep continuity, primarily sleep duration and sleep fragmentation, on daily pain in adults with sickle cell disease. Seventy-five adults with sickle cell disease completed baseline psychosocial measures and daily morning (sleep) and evening (pain) diaries over a 3-month period. Mixed-effect modeling was used to examine daily between- and within-subjects effects of sleep continuity parameters on pain, as well as the synergistic effect of sleep fragmentation and sleep duration on pain. Results revealed that nights of shorter sleep duration and time in bed, increased fragmentation, and less efficient sleep (relative to one's own mean) were followed by days of greater pain severity. Further, the analgesic benefit of longer sleep duration was attenuated when sleep fragmentation was elevated. These results suggest that both the separate and combined effects of sleep duration and fragmentation should be considered in evaluating pain in adults with sickle cell disease.

Perspective: Subjective parameters of sleep continuity (eg, sleep duration, fragmentation, and efficiency) predict clinical pain in individuals with sickle cell disease. Additionally, sleep duration should not be considered in isolation, and its association with pain may be qualified by sleep fragmentation. Research and practice should include assessments of both when addressing pain severity.

Key words: daily diaries; pain; sickle cell disease; sleep fragmentation; sleep continuity

Introduction

Sleep is disrupted among individuals with chronic pain conditions, with daily diary studies finding abnormal sleep onset (>30 minutes), fragmented sleep (1–2 awakenings during the night and for >30 minutes), and inefficient sleep (80–85% sleep efficiency).[10, 20, 21, 35]

A growing body of evidence suggests that poor sleep prospectively predicts increases in clinical and experimental pain.[8] Specifically, a limited number of studies have demonstrated that indices of sleep continuity, such as decreased sleep duration,[17, 35] delayed sleep onset latency (SOL, >30 minutes),[17, 35] and increased sleep fragmentation (ie, wake after sleep onset [WASO]) predict increased pain severity.[17] Investigations of sleep continuity are important because they provide an estimate of the association of sleep and pain that is less susceptible to retrospective heuristic biases than ratings of sleep quality, which may be influenced by feeling states present at the time of reporting.[15, 27]

A few studies have identified sleep fragmentation (eg, high WASO) as a particularly harmful characteristic of sleep continuity. Smith et al[28] demonstrated that experimentally disrupting sleep continuity (ie, increasing WASO) significantly decreased endogenous pain inhibition and increased spontaneous pain in healthy participants. In 2 observational studies, increased sleep fragmentation significantly predicted higher next-day pain among adolescents and adults with chronic pain.[1, 18] Although evidence generally supports the notion that sleep fragmentation increases vulnerability to pain, it is not known if sleep fragmentation interacts with other aspects of sleep continuity in predicting pain. For example, it would be important to know if the effects of sleep duration on pain are more pronounced or less pronounced in the context of fragmented

sleep (relative to nonfragmented sleep), thereby elucidating the value of acquiring both longer and consolidated sleep.

We elected to study sleep continuity and pain in adults with sickle cell disease (SCD) for several reasons. First, pain is the most commonly reported symptom of SCD and exhibits day-to-day variability.[19, 31] Second, up to 70% of patients with SCD report sleep disturbances, including difficulty initiating and maintaining sleep.[14, 34] Sleep continuity has not been quantified among nonsleep clinic adults with SCD; however, sleep-disordered breathing (eg, obstructive sleep apnea)[6, 9] and pain[12, 13, 33] are common etiologies. Although disturbed sleep correlates with greater SCD pain,[12, 13, 33] and sleep is impaired during a vaso-occlusive crisis,[12, 13] little is known about day-to-day variations in sleep, as well as the extent to which disrupted sleep continuity influences daily SCD pain.

Given the limitations of previous investigations, the goals of the present analyses were to examine the direct effect of parameters of sleep continuity during the night (sleep duration, latency, and fragmentation) on SCD pain experienced between waking and going to bed the following day (ie, next-day pain). We also examined the interacting, or synergistic, effect of sleep fragmentation and sleep duration on next-day pain in the course of daily life in adults with SCD. For the second goal, we hypothesized that the synergistic effect of decreased sleep duration and greater sleep fragmentation would be associated with the highest next-day pain severity.

Methods

Participants

Participants in these analyses are from a larger National Institutes of Health–funded study investigating dimensions of pain among individuals with SCD. Participants

for the parent study were recruited through SCD clinics as well as posted flyers and advertisements. Individuals with SCD were eligible to participate in the parent study if they were 1) 18 years or older, 2) diagnosed with an SCD hemoglobinopathy genotype (HbSS, HbSC, HbS/β-thalassemia), 3) on a stable dose of nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids (ie, no change in pain management regimen made by a clinician during the weeks prior to enrollment), 4) without a vaso-occlusive crisis within the past 3 weeks, and 5) willing to provide informed consent. Individuals with SCD were excluded from participation if they 1) were an active substance abuser, 2) had a significant cognitive impairment or mental disorder, 3) had current infection, 4) had received a diagnosis of an autoimmune disorder, 5) had human immunodeficiency virus infection with a neuropathy, or 6) were currently pregnant, lactating, or planned to become pregnant in the subsequent 6 months of the study. A total of 236 individuals with SCD were screened by phone for participation in the parent study; 84 were eligible after the phone screen, and 84 provided study consent.

Only participants with SCD from the parent study who completed the electronic daily diary assessment portion of the study (n = 78) were used in the present analyses. The diary assessment period was intended to be approximately 3 months; however, the total number of diary days varied among participants. We excluded participants (n = 3) who completed less than 1 week (<7 days) of diary entries and/or had a diary completion ratio (an index of diary adherence calculated as number of diaries completed out of the total number of days the participant carried the personal digital assistant) of less than or equal to 25%. At least 1 week of diaries is recommended for examining variations in sleep.[4] Additionally, large intervals between reporting days would decrease our ability to

examine day-to-day variations in sleep. In total, 75 adults (96% of all participants with SCD who completed the electronic diary portion of the study protocol) were included in the subsequent analyses.

Procedure

An institutional review board at the study site approved all study procedures. Written informed consent was obtained from each study participant at the baseline study session. During the baseline session, psychosocial measures (eg, Center for Epidemiologic Studies Depression Scale [CES-D] and Pain Catastrophizing Scale [PCS]), demographic questions, and a medical and psychiatric history were collected.

At the conclusion of the baseline session, participants were provided with and trained on the use of an electronic handheld diary. The electronic diary included 2 reporting segments (morning for sleep and evening for daily pain) and was used to record daily experiences over the subsequent 3-month period.

Measures

Daily Measures

Electronic morning (sleep) and evening (pain) diaries were completed on a personal digital assistant (Palm personal electronic organizer; Palm Inc, Sunnyvale, CA) using a customized application. Responses to each sleep and pain item were logged into customized menus and data entry screens with the use of a stylus pen. Participants did not receive daily reminders to complete entries; however, participants were scheduled for a 1-week and as-needed follow-up to answer any questions about the diary and to identify any technical issues regarding its use in order to enhance compliance with data entry

procedures. Participants received financial incentives based on the number of diaries completed.

During data cleaning, entries that were not completed within 12 hours of waking or bedtime were removed to decrease recall bias. Of the 5,839 days in which a personal digital assistant was carried across participants (average of 78 days per participant), 4,411 morning diaries (average of 59 entries per participant) and 4,549 evening diaries (average of 61 entries per participant) were included in our analysis.

Sleep Diary. Immediately on waking, participants were instructed to record what time they went to bed that night, their final awakening time, and what time they got out of bed that morning. Participants were also asked to estimate how long it took them to fall asleep (ie, SOL) and the total amount of time they spent awake during the night (ie, WASO). These variables were used to calculate sleep duration (ie, total sleep time [TST]), time in bed, and sleep efficiency for each participant. Sleep efficiency, an index of the proportionate time in bed spent asleep, was calculated as a percentage of TST to time in bed.

The reliability and validity of sleep diaries to measure parameters of sleep continuity, given the potential for recall bias, has been assessed. Overall, self-reported sleep parameters are used frequently and have been validated against objective measures.[5] Furthermore, although both individual and systematic variability in measurement exists, an assessment period of at least 3 weeks or longer for sleep diaries is sufficient to achieve accurate and stable estimates in both insomniacs and normal sleepers.[36] As noted above, each participant in the present analysis contributed an average

of 59 morning (sleep) diaries, which supports the adequacy of using sleep diaries to measure parameters of sleep continuity.

Pain Diary. Participants were instructed to record just before bed their average pain level for the day. Participants manipulated an electronic slider on the screen between 0 ("no pain") and 100 ("pain as bad as you can imagine"). Participants were also instructed to self-report the degree to which pain interfered with daytime activities and answer the question "Are you in a sickle cell [vaso-occlusive] crisis today?" As has been done in prior work, a proportion of diary days in pain (end-of-day pain rating greater than 0 out of 100, indicating some pain that day)[30] and proportion of diary days for which a vaso-occlusive crisis was reported[30] were calculated for each participant as a proxy of SCD severity.

Covariates

Demographic information, including age, gender, education level, and marital status, and information about pain medication use were collected at baseline. Additionally, participants completed questionnaires on pain catastrophizing and depressive symptom severity at baseline. Both measures were included as covariates in the present analyses because both are highly associated with clinical pain severity and sleep continuity.[3 and 23]

Depressive Symptoms. The CES-D is a self-report instrument that assesses depressive symptom severity.[24] Responses to each item are reported on a 4-point Likert-type scale from 0 ("rarely" or "none of the time") to 3 ("most" or "all of the time"). A summary total score is calculated (scores of 16 or greater suggest clinically relevant depressive symptoms).[24] The reliability of the CES-D in our sample was good

(Cronbach's alpha = .78) and is similar to estimates found in another study of adults with SCD.[16]

Pain Catastrophizing. The PCS is a 13-item scale used to measure negative cognitive-emotional appraisals of pain.[32] The PCS, which was initially validated among undergraduate students, has been subsequently validated among a sample of community-dwelling adults.[22] Each item is reported on a 5-point Likert-type scale from 0 ("not at all") to 4 ("all of the time"), where scores of 30 or greater indicate clinically relevant catastrophizing.[32] The PCS scale had excellent reliability in our sample (Cronbach's alpha = .91) and was similar to the reliability found in another study with community-dwelling adults.[22]

Data Analytic Strategy

Multilevel modeling (MLM) was used to evaluate daily between- and within-subjects effects of sleep continuity characteristics on pain and the potential moderating effect of WASO on the relationship between sleep duration and clinical pain. MLMs can account for dependencies created by repeated measurements over time on independent units (ie, the participant). The MLM approach can also distinguish between changes over time in the dependent variable both within an individual (ie, level 1) and between individuals (ie, level 2).[25]

In our first set of MLMs, we tested separate within-subjects (level 1) models specifying an independent fixed effect of sleep duration, time in bed, SOL, WASO, and sleep efficiency during the night on our dependent variable next-day pain, which was the severity of pain reported between waking and going to bed the following day. In our second set of MLMs, we tested an expanded model that included WASO, TST, and their

interaction term as independent variables predicting next-day pain severity. We allowed the intercept to vary randomly across participants for all MLMs and controlled for autoregressive correlation between observations by modeling the variance–covariance matrix using an autoregressive 1 function. Age, gender, depressive symptoms, pain catastrophizing, and opioid medication use (yes or no) were tested as between-subjects (level 2) covariates. Covariates that were not significant ($P > .20$) were removed in order to improve model fit and to achieve the most parsimonious model. All level 1 independent variables were centered at each participant's mean, whereas level 2 covariates were centered at the mean values across all participants, as recommended by Enders and Tofighi.[7]

Descriptive statistics, Spearman's rho correlations, and MLMs were all computed and performed in SPSS, version 21.0 (IBM Corp, Armonk, NY).[11]

Results

Descriptive Statistics

Seventy-five adults with SCD completed more than 1 week (>7 days) and at least 25% of their daily morning (sleep) and evening (pain) diaries over the study period. Descriptive characteristics of the study participants are displayed in Table 4.1. Overall, participants ranged from 19 to 64 years of age (mean = 38.5 years). Most of the sample was female, African American, and single and had at least a college or technical degree. The mean CES-D and PCS scores in our sample were 14.6 and 13, respectively.

Average pain severity on pain days without crisis and pain days with crisis over the study period were 32.4 and 50.7 out of 100, respectively, and are consistent with pain severity reported in previous studies.[30] Approximately 35% of participants reported pain

almost every day (>95%), whereas 11% of the sample rarely reported pain (≤5%). In addition, only 8% reported a vaso-occlusive crisis on more than 50% of their diary day, whereas almost a third of the sample (29.3%) did not report a vaso-occlusive crisis on any of their diary days. Approximately 57% of the sample reported taking some type of opioid (short and/or long acting), whereas 29% reported taking nonsteroidal anti-inflammatory drugs during the study period (Table 4.1).

Table 4.2 displays the sleep continuity characteristics of the sample. Compared to recommendations and abnormal sleep indicators for adults,[2,26] on average our sample of adults with SCD reported normal sleep duration (average of 7 hours) but abnormal sleep latency (>30 minutes), WASO (>30 minutes), and sleep efficiency (<85%). Correlations between sleep continuity indices and diary pain severity are provided in Table 4.3. Overall, mean pain severity correlated significantly with all indices of sleep continuity in the hypothesized direction.

Main Effect Models

Results of our main effect MLMs revealed, relative to the within-person mean across days, that lower TST ($\beta = -.01$, standard error [SE] = .001, $P < .001$), lower sleep efficiency ($\beta = -.03$, SE = .01, P = .02), lower time in bed ($\beta = -.004$, SE = .002, P = .01), and higher WASO ($\beta = .02$, SE = .004, $P < .001$) predicted higher next-day pain. SOL did not significantly predict next-day pain severity (P = .39). These models suggest that a 30-minute increase in total sleep time or 5% increase in sleep efficiency (above an individual's mean) is associated with lower pain severity the next day (a decrease of .30 and .15 points on a 0–100-point scale, respectively). Similarly, for every 30-minute decrease in WASO, next-day pain severity is estimated to be lower by .60 points.

Interaction Model

We tested separate MLMs that included WASO and TST as an interaction term to investigate the combined effect of sleep duration and fragmentation on pain severity (Table 4.4). In model 1, the interaction term was significant (P = .04) and suggested that next-day pain severity increases as both sleep fragmentation and sleep duration increase above an individual's norm. The small effect from the MLM may be related to variation within and between subjects. In post hoc testing, we used linear regression to estimate a mean between-subjects interaction effect as a test of the reliability of the daily interaction effect. In this model, the interaction effect was still significant (β = .001, SE = .00001, P = .04), suggesting reliability of the daily interaction of WASO and TST. However, as displayed in Fig 4.1, the effect of TST on next-day pain is attenuated by high WASO. The daily interaction effect accounted for approximately 7% of the within-subject variance in clinical pain severity (pseudo-R2 = .067). We examined whether the daily interaction effect of sleep duration and sleep fragmentation remained significant and whether model fit improved after removing covariates that were not significant (model 2). We also examined whether model fit would change if depressive symptoms were removed, because this variable decreased our sample size by 8 participants (model 3). We found no change in the magnitude, direction, or significance of the fixed effects. We also found a negligible change in model fit with the removal of nonsignificant covariates (χ2[3] = 4, P = .26), but model fit was worse with the removal of depressive symptoms (χ2[1] = 3,092, P < .001). Therefore, depressive symptoms were retained as a covariate in the final model (model 2), suggesting that even after accounting for depressive symptoms, there is a benefit to obtaining longer and consolidated sleep.

Discussion

The present study sought to examine the relationship between indicators of sleep continuity and clinical pain in a population of adults with SCD. Through the use of electronic daily sleep and pain diaries during 3 months of observation in patients' natural environment, we found that nights characterized by shorter sleep duration, more sleep fragmentation, and less efficient sleep than was typical were followed by days of higher than typical clinical pain severity. Latency of sleep had no effect on next-day pain severity. We also found a small yet significant interaction effect between sleep fragmentation and sleep duration, which supported our hypothesis that the effect of sleep duration on pain is different on fragmented versus nonfragmented days. In general, as sleep duration increases, next-day clinical pain severity decreases; however, this benefit occurs only with low levels of sleep fragmentation.

This article adds to the growing research literature highlighting sleep continuity, specifically sleep fragmentation (ie, WASO), rather than delayed sleep onset as a predictor of next-day pain severity. Similar to prior studies, we demonstrated that daily changes in sleep fragmentation and total sleep time predict variation in next-day clinical pain severity.[1, 18, 28] We also show, however, that the effects of sleep continuity should not be considered in isolation; the benefits of longer sleep may only be realized in the absence of sleep fragmentation.

Several clinical and research implications can be drawn from our results. First, to our knowledge, this is the first study to characterize the sleep continuity characteristics of adults with SCD using electronic daily diaries. Our findings suggest that it may be important for clinicians working with adults with SCD to routinely include assessments

of sleep continuity through daily diaries and discussions with patients about their sleep habits, particularly when pain is poorly controlled. These discussions should include an assessment of total sleep duration, sleep latency, sleep fragmentation (ie, minutes awake after sleep onset), and sleep efficiency (ratio of total sleep time to total time in bed). Furthermore, although the sleep duration and sleep fragmentation interaction effect was small, we find that the combination of increasing sleep duration and reducing sleep fragmentation may be most beneficial to pain reduction, which may occur through changes in central pain processing. Sleep fragmentation has already been shown to reduce endogenous opioid pain modulation in healthy adults[28] and may provide a mechanism underlying the effects of daily sleep fragmentation and sleep duration on next-day clinical pain in patients with SCD. In addition, increased sleep fragmentation and shorter sleep duration may promote hyperalgesia through increased inflammatory activity.[29] Nevertheless, the small effects observed in the present study should be considered with the qualification that they represent self-report responses observed from day to day; these small daily effects, however, may accumulate over years of coping with SCD and thus integratively represent a contributor to disease burden and poor quality of life in these patients. Future research and treatment studies should consider the interacting effects of sleep fragmentation and sleep duration and seek to determine if specifically altering sleep continuity in patients with SCD yields clinically meaningful changes in SCD pain. In addition, the interaction between sleep continuity and opioid use on clinical pain should be explored, given the known effect of opioids on sleep continuity.

There are a few notable limitations of our analyses. First, all data were self-report; no objective measures of sleep were obtained. However, self-reported sleep parameters are used frequently and have been validated against more objective measures.[5] Nonetheless, future work may integrate objective sleep measurement in the home with intensive longitudinal self-report data. Second, the exclusive focus on SCD pain in our analysis limits the generalizability of our findings to other pain populations. Third, nearly 25% of both morning (sleep) and evening (pain) diaries were missing. The adherence rate of approximately 75% is consistent with earlier work and is reasonable considering the number of participants and length of the assessment period. Furthermore, our analytic method (MLM) is fairly robust to missing data.

Finally, the parent study sampled adults with SCD who were on a stable pain management regimen, free of infection, and relatively stable in terms of the management of their SCD. Thus, it is possible that our sample is healthier than the population norm for SCD. However, we found that approximately one-third of the sample (35%) reported pain almost every day during the study period (similar to Smith et al[30]). This finding supports the notion that SCD pain in the general public and in our population is common.[30, 31]

Despite these limitations, our investigation has a number of strengths. A major strength is the emphasis on daily reports of sleep and pain using electronic diaries, which have become the gold standard for measuring time-varying fluctuations in daily life. Additionally, we followed participants for up to 3 months, which provided an extensive and thorough assessment period through which the relationship between sleep and pain could be reliably estimated. Finally, we had a sufficiently large sample size of

participants with SCD (N = 75) who collectively provided more than 4,000 records of daily sleep and pain diaries during the assessment period.

Conclusion

Overall our results suggest that parameters of sleep continuity (ie, sleep duration, sleep fragmentation, and sleep efficiency) are predictors of clinical pain severity in individuals with SCD. Furthermore, sleep duration should not be considered in isolation, and its daily association with SCD pain may be qualified by the amount of sleep fragmentation present. Therefore, clinicians and researchers working with pain populations should include assessments and interventions targeting sleep continuity, with a focus on both sleep duration and sleep fragmentation, when addressing pain in SCD.

Acknowledgements

Supported by grants from the National Institutes of Health: National Heart, Lung, and Blood Institute Investigator Grant 5R01HL098110 (J.A.H.) and National Institute of Nursing Research Predoctoral Training Fellowships T32NR012704 and F31NR014598 (G.M.-J.).

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Figure 4.1. Moderation of the within subjects effect of sleep duration on clinical pain by sleep fragmentation (adjusted)

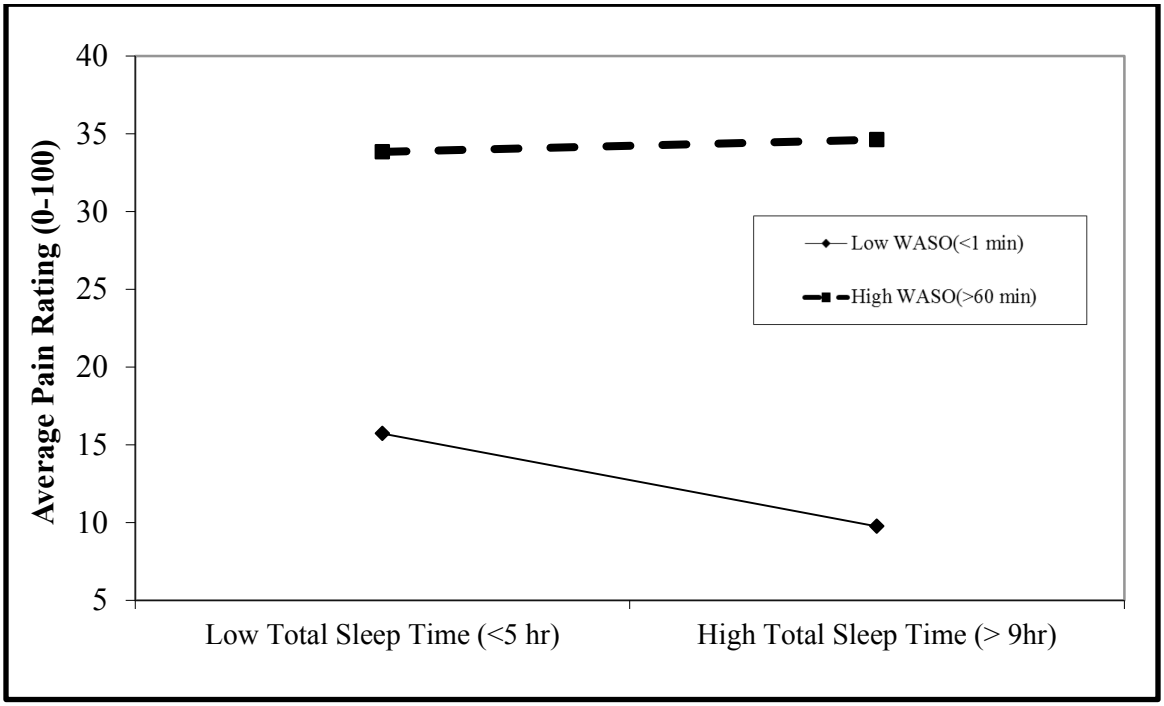

Table 4.1. Sample demographic, psychosocial, and pain characteristics (N = 75)

Characteristic	Mean (SD)	*n* (%)
Demographic		
Age, years	38.5 (11.8)	
Female		54 (72.0)
African-American		75 (100.0)
Marital Status		
Married/Cohabitating		23 (30.6)
Single		42 (56.0)
Separated/Divorced		10 (13.3)
Education		
High School or less		11 (14.7)
Some College		28 (37.3)
Tech School/College Grad		28 (37.3)
Master/Doctoral Degree		8 (10.7)
Pain		
Percentage of diary days with pain†	63% (1%-100%)	
≤ 5%		8 (10.7)
6%-49%		22 (29.3)
50%-95%		19 (25.3)
> 95%		26 (34.7)
Percentage of diary days with VOC†	6% (0%-88%)	
0%		22 (29.3)

1%-49%		47 (62.6)
≥50%		6 (8.0)
Opioid Use		43 (57.3)
NSAID Use		22 (29.3)
Psychosocial		
CESD‡	14.6 (10.9)	
PCS‡	13 (9.3)	

Abbreviations: M, mean; SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug; VOC, vaso-occlusive crisis.

† Across participants over the study period

‡ n < 75 due to missing value

Table 4.2. Sleep continuity characteristics of the sample (N = 75)

Sleep Parameter	M (SD)*	Range*
Total Sleep Time, hr	7.0 (2.2)	1.9 – 19.5
Time in Bed, hr	8.6 (2.0)	5.8 – 20.8
Sleep Onset Latency, min	35.5 (35.4)	1.60 – 190.9
WASO, min	32.2 (35.8)	0.1 – 242.0
Sleep Efficiency, %	81.4 (14.2)	24.0 – 97.0

M = mean; Min = Minutes; SD = Standard Deviation

* Computed from participant mean sleep continuity characteristics

Table 4.3. Correlations of primary study variables

	Variables					
	1	2	3	4	5	6
1. Mean TST	1	.56**	-.47**	-.50**	.59**	-.31**
2. Mean TIB		1	.01	.21	-.14	.24*
3. Mean SOL			1	.63**	-.70**	.41**
4. Mean WASO				1	-.76**	.66**
5. Mean sleep efficiency					1	-.54**
6. Mean Pain Severity						1

* $p < 0.05$

** $p < 0.01$

Table 4.4. Multilevel model of TST and WASO predicting daytime clinical pain severity

	Model 1	**Model 2**	**Model 3**
Fixed effects	**β (SE)**	**β (SE)**	**β (SE)**
Intercept	31.7(3.0)***	20.7 (4.0)***	33.1(2.7)***
WASO	.02(.01)***	.02 (.01)***	.02(.01)***
TST	-.005(.002)**	-.005 (.002) **	-.004(.002)*
TST x WASO	$2.8E^{-5}(1.4E^{-5})$*	$2.8E^{-5}(1.4E^{-5})$*	$2.8E^{-5}(1.4E^{-5})$*
Opioid nonuse†	-20.9(4.2)***	-20.5 (4.1)***	-23.3(4.2) ***
CES-D	.55(.21)**	.6(.2)**	
PCS	.23(.24)		
Age	.06(.17)		
Male††	-4.6(4.7)		
Random Effects			
Intercept	247.1(46.5)***	241.9 (44.4)***	306.0(52.7) ***
Deviance	27,048.6	27,052.3	30,144.3
AIC	27,054.6	27,058.3	30,150.3
BIC	27,072.9	27,076.7	30,169.0

Abbreviations: SE, standard error; AIC, Akaike information criterion; BIC, Bayesian information criterion.

NOTE. CES-D: grand mean centered; PCS: grand mean centered; TST: person centered; TST × WASO: person centered; WASO: person centered.

† Relative to opioid use. †† Relative to Females

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$

CHAPTER FIVE: DISCUSSION

Introduction

Sleep disturbances and insomnia symptoms are common in patients with chronic diseases (National Center on Sleep Disorders Research, 2003). Sleep disturbances have been associated with multiple negative psychosocial and physiological outcomes including worsening pain (Buenaver et al., 2012; Tanabe et al., 2010), increased unscheduled health care utilization, and health care costs (Daley et al., 2009; Foley, Sarsour, Kalsekar, & Walsh, 2010), and decreased quality of life (Colten, Bruce M. Altevogt Editors, & Research, 2006; Long, Krishnamurthy, & Palermo, 2008; Palermo & Kiska, 2005). In adults with sickle cell disease (SCD), the prevalence and outcomes of sleep disturbances are just beginning to be explored. The purpose of this study was to examine sleep disturbances, specifically insomnia symptoms, among adults with SCD in order to contribute to the existing symptoms science research in this population.

In this chapter, the results of this study are summarized. Both the main findings and exploratory findings are discussed and are organized by study aim. Following the results, is a discussion about the strengths and limitations of this study. Implications for research and practice are also discussed.

Main Findings

The ISI is a brief 7-item instrument that is used to evaluate insomnia symptoms (Bastien, Vallières, & Morin, 2001) and was a primary instrument used in this study to measure insomnia symptoms. It was important to begin this study by establishing the reliability and validity of the Insomnia Severity Index (ISI) in adults with sickle cell disease (SCD), which had not be done to-date. Exploratory factor analysis, construct

validity, and internal consistency reliability were used to determine the validity and reliability of the ISI for evaluating insomnia symptoms among adults with SCD. Findings from the psychometric evaluation established the overall reliability and validity of the ISI for use in adults with SCD. In addition, although often used as a unidimensional measure in research, this study also identified two distinct factors *insomnia symptoms* (Items 1-3) and *insomnia impact* (Items 4-7), which can and should be used in future research and practice to examine distinct aspects of the symptom experience in this population.

Aim 1. Identify the situational, psychological, and physiologic factors that are associated with insomnia symptoms in adults with sickle cell disease.

This portion of the study used a prospective cohort of 263 adults with SCD from the Improving Patient Outcomes with Respect and Trust (IMPORT) study to identify bio-psychosocial predictors of insomnia symptom severity. First, this study found that insomnia symptoms were common and severe among adults with SCD. Using the unidimensional Insomnia Severity Index, a slight majority (55%) of the sample reported clinically significant insomnia symptomatology (ISI $\geq$10), while 41% reported a level of insomnia symptom severity that suggests they may have an insomnia disorder (ISI $\geq$14). Overall, we found that acute pain severity and depressive symptomatology were the only independent predictors of insomnia symptom severity among this sample of adults with SCD.

Aim 2. Examine the relationship between sleep duration, sleep onset latency, sleep fragmentation and clinical pain in adults with sickle cell disease.

This study was an analysis of daily sleep and pain diaries in adults with SCD. The sleep diary was used to examine specific parameters of sleep continuity including sleep duration, sleep onset latency (i.e. time it takes to fall asleep), and sleep fragmentation (i.e. the frequency and amount of time an individual is awake after sleep onset). While sleep diaries are not diagnostic, they do provide daily information about individual sleep patterns, specifically information that can also be used to look at insomnia symptoms including difficulty falling asleep and staying asleep.

The results of this study revealed that subjective parameters of sleep continuity predicted clinical pain severity. Specifically, predictors of increased clinical pain severity in adults with SCD were shorter sleep duration, increased sleep onset latency, and increased sleep fragmentation compared that individual's norm. As an additional analysis, this study also found that the analgesic benefits of sleep duration may be moderated by sleep fragmentation. That is, at increased levels of sleep fragmentation (above an individual's norm) the analgesic benefits of obtaining longer sleep is attenuated.

Additional Findings

Aim 3. Examine the relationship between insomnia symptom severity and perceived quality of life in adults with sickle cell disease.

Aim 4. Examine the relationship between insomnia symptom severity and unscheduled acute care utilization in adults with sickle cell disease.

Increased healthcare utilization (Daley et al., 2009; Foley et al., 2010) and decreased quality of life (Colten et al., 2006; Long et al., 2008; Palermo & Kiska, 2005)

are two outcomes associated with sleep disturbances and insomnia symptoms, but neither has been examined among adults with SCD. Since, approximately 20% of individuals with SCD are considered frequent healthcare utilizers (C. P. Carroll, Haywood, Fagan, & Lanzkron, 2009; C. P. Carroll, Haywood, & Lanzkron, 2011), it is important to explore whether insomnia symptoms are an independent risk factor or if insomnia symptoms explain some of the variance in unscheduled use of healthcare resources. Equally important is examining whether sleep disturbances or insomnia symptoms are associated with negative quality of life, which also has not been examined in adults with SCD. Because of methodological challenges inherent in both outcomes, the final two aims (Aims 3 and 4) were exploratory and are presented below. The goal of these two aims was to expand the research on the potential impact of sleep disturbances, specifically insomnia symptoms in adults with SCD.

Methods

Participants

Participants from the Improving Patient Outcomes with Respect and Trust (IMPORT) study were used in the analysis of Aims 3 and 4. Briefly the IMPORT cohort was comprised of a convenience sample of 291 participants (≥15 years) with SCD who resided in the greater MD/DC metropolitan area. For Aims 3 and 4, individuals from the parent study who self-identified as 18 years of age or older at their baseline visit (100% African American) were included.

Primary Measures

The 7-item *Insomnia Severity Index* was used to evaluate insomnia symptom severity. Baseline summary scores from the unidimensional instrument were used in the analysis of both aims.

The *Short Form Health Survey (SF-12)* is a measure of perceived functional health and well-being (J. Ware, Kosinski, & Keller, 1996). Among the 12-item scale, a single *general health* scale-item can be used to assess one's perceived health status, which is a component of perceived quality of life. This item does not have a recall period thus can be used to measure both acute and long-term general health evaluations. Responses are reported on a five-choice Likert scale with options of *Poor*, *Fair*, *Good*, *Very Good*, and *Excellent*. For the analysis of Aim 3, the baseline general health item was dichotomized into *Poor/Fair* and *Good/Very Good/Excellent*, which under norm-based scoring (0-100 scale) corresponds with perceived *below average* and *above average* health, respectively (J. E. Ware, Kosinki, Turner-Bowker, & Gandek, 2002).

Participants self-reported how many times they used acute care services (i.e. emergency room or infusion center) for both sickle cell crisis and non-crisis pain over the 6 month period following the baseline visit. Response choices were *none*, *1-2*, *3-5*, *6-10*, and *more than 10 times* over the previous 6 months. Frequency of *unscheduled acute care utilization* for pain was dichotomized into <3 times and ≥3 times in the past 6 months to separate low from high frequency healthcare utilizers. The cut-point chosen for low versus high utilizers was based on definitions used in previous studies (Aisiku et al., 2009; C. P. Carroll et al., 2009; P. C. Carroll, Haywood, Hoot, & Lanzkron, 2013).

Pain, depressive symptoms, and SCD genotype, if significantly associated with the outcome of interest, were included as covariates in the analyses as they are related to

unscheduled acute care utilization and perceived health status. A single self-report item "Do you have daily chronic pain" was used to measure the presence or absence of c*hronic pain*. This item was not bound by a time period and response options were *no* or *yes*. This item has been used in previous studies by the IMPORT group and is a reliable measure with good discrimination between individual who do and do not experience daily chronic pain (Haywood et al., 2014). *Center for Epidemiology Studies in Depression (CESD-10)* was used to measure the degree of depressive symptomatology experienced over the previous week (Andresen, Malmgren, Carter, & Patrick, 1994). In general, higher total scores across items indicate a greater degree of depressive symptomatology. *SCD genotype* was extracted from the participant's medical record and was recorded as: *HbSS*, *HbSC*, *HbS/β^0-Thalassemia*, and *HbS/β^+-Thalassemia*.

Analysis

Logistic regression was used to assess the predictive power and relative contribution of insomnia symptom severity to both perceived health status and unscheduled acute care utilization. Chronic pain, depressive symptomatology, and SCD genotype, if determined to be associated with each outcome, were controlled for in the subsequent analysis. Statistical significance was set at a probability of less than 0.05. All analyses were performed in Stata 13 software (StataCorp, 2013).

Results

Results of this analysis revealed that among 252 participants from the IMPORT study, a slight majority (51%) rated the health as *below average*. Insomnia symptom severity was significantly higher among individuals who rated their health as *below average* (i.e. Poor or Fair) as compared *above average* (i.e. Good to Excellent; mean

difference = 5.2 points, $p < 0.01$). However, the odds of perceiving one's health as "above average" was only a non-significant trend (OR = 0.95, 95% CI 0.95 – 1.0, p = 0.067), after controlling for the presence of daily chronic pain and depressive symptoms (Table 5.1). SCD genotype was not associated with perceived health status (p = 0.22), thus not included in the analysis.

Table 5.1. Predictors of perceived general health*

Variable	OR (95% CI)	p-value
Insomnia symptom severity (ISI)	0.95 (0.90-1.0)	0.067
Chronic Pain	0.37 (0.20-0.66)	0.001
Depressive symptoms	0.92 (0.86-0.99)	0.02

* 252 participants from the IMPORT study

Due to attrition between the baseline and six month follow-up visit, only 195 participants (≥18 years) from the IMPORT study were included in the analysis of Aim 4. Among the 195 participants, approximately 36% (n = 70) were considered high ED users (≥ 3 unscheduled acute care visits over a 6 month period), which is higher than the approximately 20% of high utilizers found in other studies (C. P. Carroll et al., 2009, 2011). Nevertheless, results revealed that SCD genotype was not associated with utilization (p = 0.78), but insomnia severity was significantly higher among individuals who were high ED users as compared to low ED users (< 3 unscheduled acute care visits over a 6 month period; mean difference = 2.9 points, p = 0.01). In addition, the odds of being a high ED utilizer increased by 4% for every one-point increase in insomnia symptom severity (OR = 1.04, 95% CI 1.002 - 1.1, p = 0.037) even after controlling for

the presence of daily chronic pain over the 6 month period (Table 5.2). Overall, exploratory results suggested that insomnia symptom severity is an independent predictor of healthcare utilization even after controlling for pain.

Table 5.2. Predictors of acute care utilization*

Variable	OR (95% CI)	p-value
Insomnia symptom severity (ISI)	1.04 (1.0 – 1.1)	0.04
Chronic Pain	2.33 (1.23-4.4)	0.01

* 195 participants from the IMPORT study

Strengths and Limitations

Limitations

This study has several important limitations, many of which are related to conducting a secondary analysis of data. The primary limitations pertain to 1) generalizability and 2) measurement. Each of these limitations is discussed in further detail below.

First, the ability to generalize the findings of this study to other adults with SCD may be limited because both prospective cohorts used in this study consisted of a non-probabilistic convenience sample of participants approached at metropolitan hospitals and outpatient clinics on the East Coast of the United States (US). It is possible that participants in both cohorts do not represent the attitudes, beliefs, and sleep and insomnia-related symptom experiences of other adults with SCD living throughout the US. However, despite the sampling method used in both parent studies, the majority of participants self-identified as African-American, which mirrors the population of patients

with SCD in the US. Therefore, the experiences reported by the participants in this study are likely similar to that of many adult patients with SCD.

Another inherent limitation of this study is measurement, specifically the measurement of sleep disturbances and insomnia symptoms. The ability to accurately assess the sleep experience of adults with SCD, in this study, hinges upon the methods used to quantify their symptom experience. The gold-standard for diagnosing insomnia is a clinician interview (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008), however in this study, the ISI and a sleep diary were used. Further, the ISI was only collected at baseline in the IMPORT study and while the ISI does have adequate test-retest reliability (Chung, Kan, & Yeung, 2011; Savard, Savard, Simard, & Ivers, 2005), the correlation between re-test periods is known to decrease over time (Savard et al., 2005). Despite the limitations of the ISI, a strength of this study was the ability to examine sleep characteristics in adults with SCD using daily sleep diaries over a period of three months in the Clinical Implications of Pain Phenotypes in Sickle Cell Disease cohort. Daily sleep diaries have become a gold standard for measuring time-varying characteristics in sleep (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006), thus have the ability to provide a reliable assessment of sleep characteristics among adults with SCD. As a post-hoc exploration, this study examined sleep characteristics obtained using sleep diaries in the Clinical Implications of Pain Phenotypes in Sickle Cell Disease study and the insomnia symptom experience reported by participants in the IMPORT study. From this examination, it was evident that adults with SCD from both cohorts showed signs of insomnia symptoms, namely difficulty initiating sleep (sleep onset latency greater than 30

minutes) and maintaining sleep (sleep fragmentation greater than 30 minutes), that appear to persist over time (data provided in Appendix A).

Strengths

Despite the limitations, there are a few notable strengths. First, this study is one of the first to systematically and rigorously explore insomnia symptoms among adults living with SCD, thus the finding that sleep is impaired and symptoms of insomnia are prevalent is a major contribution to the literature.

This study also used data from two different cohorts of adults with SCD to explore sleep disturbances and insomnia symptoms in this population. The results from both cohorts, while using different methodologies, suggested sleep is impaired and insomnia symptoms are common thus increasing the validity of the findings found in each study.

Further, this study included data from daily electronic sleep and pain diaries, which were obtained from the Clinical Implications of Pain Phenotypes in Sickle Cell Disease Study. By using data from daily electronic diaries, this study was able to use daily diaries to begin to tease out the sequential and longitudinal relationship between sleep and pain in adults with SCD.

Finally, study sample size from both cohorts provided a sufficiently large sample for examining the aims of this dissertation, suggesting this study was adequately powered. An observed power analysis with recommendations for future studies is presented in Appendix B.

Implications

As the population of individuals with SCD ages, it is important that clinicians and researchers identify and manage symptoms that individuals with SCD experience across the lifespan. The results of this study highlighted that sleep disturbances, specifically insomnia symptoms, are prevalent and likely responsible for distressing symptoms resulting in negative outcomes including increased pain, healthcare utilization, and decreased perceived health status. However this study was a first step and should be used as springboard for future research and practice discussion as outlined below.

Implications for Research

Given the results and limitations of this study, there are several important implications for research. First, studies that examine sleep should include well validated measures and focus on specific symptoms of sleep disorders such as insomnia symptoms rather than generic sleep disturbances or sleep quality, which have been done in previous research. Studies that focus on specific sleep disturbances including insomnia symptoms will facilitate better comparisons between studies as well provide information about specific areas of sleep in need of an intervention. In this study, we found that the ISI is a valid and reliable measure of insomnia symptoms among adults with SCD. We also found that the ISI can be used to examine two distinct aspects of insomnia, *insomnia symptoms* and *insomnia impact* (Manuscript One). Therefore, future research that examines insomnia symptoms should use the ISI and explore the impact of interventions on one or both aspects of the symptom experience. In addition to the ISI, other valid measures of insomnia symptoms including clinician interview and sleep diaries can be used. Sleep diaries, in particular, provide a measure of day-to-day variation in sleep and can be useful for quantifying insomnia symptoms (e.g. number of minutes it takes to fall

asleep and chronicity of this impairment). If sleep diaries, which have been validated for use in chronic pain populations (Haythornthwaite, Hegel, & Kerns, 1991) are used, at least one week of diary data is recommended for examining day-to-day variations in sleep (Buysse et al., 2006).

While support for a randomized control trial intervention to treat insomnia symptoms may be premature, the current study provides convincing evidence that an assessment of sleep disturbances, specifically insomnia symptoms, should be included in current and future studies in adults with SCD. Current and future studies should continue to explore potential risk factors and outcomes of insomnia symptoms in this population in order to improve quality of life across the lifespan. In the meantime, given the strong relationship between pain and depression, currently funded pain and depression interventions in this population could add insomnia symptom measures and assess the effect of the intervention on insomnia symptomatology as a secondary outcome.

Implications for Nursing and Clinical Practice

Since sleep is impaired and insomnia symptoms are common among adults with SCD, clinicians should be trained and educated on the symptoms and management of sleep-impairments in this population. While all clinicians are responsible for assisting with symptom management, nurses are particularly well positioned to identify, educate, and design and implement treatment therapies for this population. Nurses are front-line providers of both acute and chronic care for all patient populations and are extremely influential in improving outcomes especially in specialized urgent-care centers such as adult Sickle Cell Infusion Clinics where patient-centered care for patients with SCD can be provided (Whiteman et al., 2014).

On intake to any clinical facility, but specifically specialized urgent-care centers and outpatient clinics, clinicians should screen for sleep disturbances including insomnia symptoms as they do for other symptoms such as pain. As found in this study, brief (7-item) validated instruments including the Insomnia Severity index can be self-administered or questions can be asked during a clinical interview to determine if sleep impairments are present and whether the impairment is acute or chronic. Other patient characteristics such as pain severity and presence of depressive symptoms should be simultaneously assessed as both were risk factors in this study and others studies in this population (Buenaver et al., 2012; Tanabe et al., 2010). Management of sleep disturbances and insomnia symptoms will vary depending upon the chronicity of the impairment. But sleep disturbance management should also include treatment of underlying causes as well as non-pharmacological management or pharmacological management if needed.

Conclusion

This study found that adults with SCD experience sleep disturbances and specifically insomnia symptoms, which may be unpleasant and distressing. The findings in this study also provide evidence that improving sleep patterns and insomnia symptoms may significantly improve quality of life, pain severity, and may decrease healthcare utilization. The main and exploratory findings in this study support assessing and treating of sleep disturbances, specifically insomnia symptoms, in adults living with SCD.

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APPENDIX A: DESCRIPTIVE SLEEP CHARACTERISTICS

Table A.1. Percentage of respondents (N=263) who endorsed each item on the Insomnia Severity Index

(Dataset: Improving Patient Outcomes with Respect and Trust)

Item	Response Options				
	0	1	2	3	4
1. Difficulty falling asleep	25.1%	24.3%	22.8%	19.4%	8.4%
2. Difficulty staying asleep	24.0%	24.7%	28.5%	16.7%	6.1%
3. Problem waking up to early	34.2%	22.1%	24.3%	14.8%	4.6%
4. Satisfaction with current sleep pattern	11.8%	13.7%	24.3%	28.1%	22.1%
5. Interference with daily functioning	18.6%	27.0%	27.4%	17.5%	9.5%
6. Noticeability of sleep problem	33.5%	25.9%	26.2%	7.6%	6.8%
7. Worry about current sleep problem	37.6%	21.8%	25.1%	7.6%	8.0%

Note:

Items 1 – 3: 0 (“none”) to 4 (“very severe”)

Item 4: 0 (“very satisfied”) to 4 (“very dissatisfied”)

Items 5-7: 0 (“Not at all”) to 4 (“very much”)

Table A.2. Mean sleep continuity characteristics across the diary reporting period (Dataset: Clinical Implications of Pain Phenotypes in Sickle Cell Disease Study)

Subject	Total Number Sleep Diary Entries	Sleep Continuity Characteristic			
		Sleep Onset Latency (mins)	Wake After Sleep Onset (mins)	Total Sleep Time (hrs)	Sleep Efficiency (%)
100	42	13.54	4.63	7.11	88
101	68	63.75	26.54	6.15	77
102	75	31.56	43.59	4.69	66
103	9	92.78	66.11	6.83	68
104	32	109.76	63.45	3.36	50
105	70	28.41	25.29	7.73	87
107	49	28.70	61.67	7.96	84
108	37	102.73	91.18	5.33	50
109	76	7.08	6.12	8.18	90
110	28	45.89	87.32	6.20	68
111	66	66.62	49.85	5.34	65

112	72	31.18	10.35	7.12	81
113	68	26.12	45.97	5.44	53
114	70	55.17	74.57	5.73	62
115	60	81.15	70.66	5.69	68
116	59	12.97	20.85	8.20	92
117	80	28.13	33.19	19.49	88
119	68	15.22	7.61	6.12	93
120	51	127.17	55.54	4.46	58
121	14	58.21	96.07	6.68	62
122	82	3.84	12.26	11.80	93
123	79	7.22	3.48	7.96	96
124	82	9.57	5.12	8.33	96
125	74	48.36	73.97	6.52	66
126	42	32.38	31.55	7.00	80
127	49	25.20	29.41	6.81	83
128	14	13.21	21.79	9.65	92

129	13	46.92	16.15	5.29	75
132	67	18.88	7.99	7.55	91
133	72	1.60	9.31	7.01	95
134	88	8.18	6.42	7.19	96
135	75	60.21	17.16	5.98	78
136	74	12.38	32.85	6.22	82
137	12	190.91	242.00	1.87	96
138	35	20.43	47.94	5.12	59
139	22	4.77	17.73	6.76	91
140	77	33.75	18.06	6.14	83
144	54	23.80	3.70	7.27	93
145	56	14.82	19.02	9.57	89
146	35	39.86	27.22	9.35	85
147	80	18.94	32.50	6.07	84
148	31	17.19	78.91	6.42	75
149	74	12.84	42.64	8.33	88

150	82	23.08	38.97	7.00	85
151	81	50.62	20.00	7.90	74
152	10	33.41	41.59	5.20	78
153	9	84.00	62.00	5.22	74
154	80	49.61	53.96	2.26	24
155	78	7.92	12.86	6.81	92
200	54	4.26	5.46	7.77	97
201	25	12.20	9.20	9.41	86
202	68	11.71	.14	6.94	96
203	80	2.50	15.50	7.36	94
204	60	5.75	3.00	10.97	97
205	76	10.20	11.60	6.84	93
206	78	35.47	22.29	4.80	64
207	33	23.09	25.30	6.40	83
208	72	38.72	9.53	8.18	88
209	63	5.16	33.33	5.83	71

210	76	42.96	33.82	6.63	83
211	42	14.40	2.74	8.25	95
212	77	20.97	8.83	6.19	90
213	70	20.00	31.74	6.48	86
214	83	37.83	14.58	7.24	84
215	72	81.32	2.29	8.64	84
216	74	9.12	10.88	6.72	89
218	64	24.22	16.02	6.22	88
219	10	60.22	.65	6.53	93
220	72	4.65	1.92	6.79	96
221	72	5.49	1.39	8.00	91
222	84	17.74	14.58	6.04	90
223	78	1.60	.71	7.63	94
224	62	130.69	83.75	6.17	58
225	79	14.62	3.48	8.15	93
400	66	90.45	82.24	8.73	74

Note: HRS = Hours; MINS = Minutes

APPENDIX B: OBSERVED POWER ANALYSES

Below are tables demonstrating the effect sizes for the relationships explored in this study. The power analyses below are presented to provide recommendations for future studies based on observed effect sizes from this study. Effect sizes and power for bivariate unadjusted relationships found in this study are presented for aims 1-3. A one-tailed hypothesis with an alpha error probability of 0.05 was assumed. G*Power Version 3.1.5 was used for all observed power analyses (Erdfelder, Faul, & Buchner, 1996).

Aim 1: Identify the situational, psychological, and physiologic factors that are associated with insomnia symptoms

Table B.1. Observed power analysis for Aim 1 (N = 263)

	Observed Effect Size	**Sample Size**	**Alpha Level**	**Power**
Age	ρ = 0.06	Original	0.05	0.26
Gender	d = 0.04	Original	0.05	0.09
Education	d = 0.34	Original	0.05	0.73
SCD Genotype	**d = 0.34**	**Original**	**0.05**	**0.82**
Disability Status	**d = 0.40**	**Original**	**0.05**	**0.94**
Urban Life Stress	**ρ = 0.45**	**Original**	**0.05**	**> 0.99**
Depressive Symptoms	**ρ = 0.68**	**Original**	**0.05**	**> 0.99**
Chronic Daily Pain	**d = 0.77**	**Original**	**0.05**	**> 0.99**
Acute Pain Severity	**ρ = 0.41**	**Original**	**0.05**	**> 0.99**

Note: Dependent variable = *Insomnia Severity Index*. SCD = sickle cell disease.

Aim 3. Examine the relationship between insomnia symptom severity and perceived quality of life.

Table B.2. Observed power analysis for Aim 3 (N = 263)

	Observed Effect Size	**Sample Size**	**Alpha Level**	**Power**
Insomnia Symptomatology	**d = 0.8**	**Original**	**0.05**	**> 0.99**

Note: Dependent variable = perceived quality of life. OR = odds ratio; SCD = sickle cell disease.

Aim 4. Examine the relationship between insomnia symptom severity and unscheduled acute care utilization for pain.

Table B.3. Observed power analysis for Aim 4 (N = 195)

	Observed Effect Size	Sample Size	Alpha Level	Power
Insomnia Symptomatology	**d = 0.42**	**Original**	**0.05**	**0.90**

Note: Dependent variable = unscheduled acute care utilization. OR = odds ratio; SCD = sickle cell disease.

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EDUCATION

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PUBLICATIONS

Journal Articles (peer-reviewed) (*indicates data based)

1. ***Moscou-Jackson G**, Finan PH, Campbell CM, Smyth JM, Haythornthwaite JA. The Effect of Sleep Continuity on Pain in Adults with Sickle Cell Disease. *J Pain*. 2015 Apr 1. pii: S1526-5900(15)00603-3. doi: 10.1016/j.jpain.2015.03.010. [Epub ahead of print] PubMed PMID: 25842346.

2. *Stephens, J., **Moscou-Jackson, G.**, Allen, J.Young Adults, Technology, and Weight Loss: A Focus Group Study. *J Obes*. 2015; 2015:379769. doi: 10.1155/2015/379769. [Epub ahead of print] PubMed PMID: 25789170.

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PRESENTATIONS

1. ***Moscou-Jackson, G.**, Haythornthwaite, J. (poster presentation). "Differences in Sleep Continuity between Crisis and Non-Crisis Pain Days In Adults With Sickle Cell Disease."29th Annual Meeting of the Associated Professional Sleep Societies, Seattle, WA. June 6-10, 2015.

2. ***Moscou-Jackson, G.**, Campbell, C., Finan, P. Haywood, C, Carroll, P, Haythornthwaite, J. (poster presentation). "Identifying central sensitization in adults with sickle cell disease: differences in clinical features and psychobehavioral factors." 34th Annual Scientific Meeting of the American Pain Society, Palm Springs, CA. May 13-16, 2015.

3. ***Moscou-Jackson, G.,** Haythornthwaite, J., Campbell, C., Finan, P. (invited poster presentation). "The Moderating Effect of Sleep Fragmentation on the Association of Sleep Duration and Pain in Adults with Sickle Cell Disease." 9th Annual NIH Pain Consortium Symposium: Advances in Pain Research, Bethesda, MD. May 28-29, 2014.

4. ***Moscou-Jackson, G.,** Haythornthwaite, J., Campbell, C., Finan, P. (poster presentation). "The Moderating Effect of Sleep Fragmentation on the Association of Sleep Duration and Pain in Adults with Sickle Cell Disease." 33rd Annual Scientific Meeting of the American Pain Society, Tampa, FL. April 30-May 3, 2014.

5. ***Moscou-Jackson, G.,** Haythornthwaite, J., Carroll, P., Bediako, S., Bond, K., Finan, P. (poster presentation). "Adaptive positive affect regulation attenuates the effect of poor sleep on pain in Sickle Cell Disease." 33rd Annual Scientific Meeting of the American Pain Society, Tampa, FL. April 30-May 3, 2014.

6. ***Moscou-Jackson, G.**, Haywood, C. Jr. (oral presentation). "Sleep in African-American adults with Sickle Cell Disease." 41th Sickle Cell Disease Association of America (SCDAA) Annual Meeting, Baltimore, MD. September 24-27, 2013.

7. ***Moscou-Jackson, G.**, Haywood, C. Jr. (poster presentation). "Sleep in African-American adults with Sickle Cell Disease." Council for the Advancement of Nursing Science (CANS) 2013 Special Topics Conference. October 6, 2013.

8. ***Moscou-Jackson, G.**, Xu, J., Mbah, O., Saleem, H., Wenzel, J., Ford, J. (poster presentation) "Staying Ahead of the Game" A Model of Clinical Trial Decision-making Informed by African American Cancer Patients. Science of Eliminating Health Disparities Summit, Washington, DC. December 17-19, 2012.

HONORS AND AWARDS

2014	Young Investigator Travel Award, American Pain Society
2009	Sigma Theta Tau, the International Nursing Honors Society, Nu Beta Chapter
2008	FULD Research Fellowship, Johns Hopkins University School of Nursing
2008	Provost Undergraduate Research Award, Johns Hopkins University School of Nursing
2007	Cancer Research Training Award, National Cancer Institute

EDITORIAL ACTIVITIES

2015 Reviewer for Journal of Health Psychology

2013 Ad hoc reviewer for Progress in Transplantation Journal (with faculty mentor)

2013 Ad hoc reviewer for Journal, Advances in Nursing Doctoral Education & Research (with faculty mentor)

PROFESSIONAL ACTIVITIES

Professional Memberships

2013-Present American Pain Society

2013-Present American Association of Sleep Medicine

2012-Present Sickle Cell Disease Association of America

LEADERSHIP/SERVICE EXPERIENCE

2014-2015 PhD Student Doctor of Philosophy Board Representative (Selected), Johns Hopkins University

2013-2014 PhD Curriculum Committee Student Representative (Elected), Johns Hopkins University School of Nursing

2011-2012 Social Chair (Elected), Doctoral Student Organization Johns Hopkins University School of Nursing

2008-2009 President, National Student Nurses Association (NSNA), Johns Hopkins University School of Nursing, Baltimore, MD

PART II

EDUCATIONAL ACTIVITIES

Classroom Instruction
Johns Hopkins University School of Nursing, Baltimore, MD

Semester	Course	Lecture Topic(s)	Level	Role
Fall 2014	Statistical Literacy and Reasoning in Nursing Research	• Sampling Methods • Research Designs • Correlations and Regression • Epidemiology	Masters	Teaching Assistant
Summer 2014	Pathophysiology	• Hematologic Disorders	Undergraduate	Teaching Assistant
Spring 2014	Statistical Literacy and Reasoning in Nursing Research	• Sampling Methods • Research Designs • Epidemiology	Masters	Teaching Assistant
Spring 2013	Research Process in Nursing	• Power Analysis • Sampling Plans	Undergraduate	Teaching Assistant
Fall 2012	Research Process in Nursing	• Power Analysis • Sampling Plans	Undergraduate	Teaching Assistant

International Classroom Instruction
Peking Union Medical College – School of Nursing, Beijing, China

Semester	Course	Lecture Topic(s)	Level	Role
Summer 2014	Introduction to Grant Writing and Writing for Publication Workshop	• Conceptual Frameworks • Research Funding • Measurement • Manuscript preparation	Post-Doctorate	Co-Instructor

Tutoring

2012-2013 Biostatistics tutor for PhD Program, JHU School of Nursing, Baltimore, MD