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Use of Medications and Services for the Management of Sickle Cell Disease

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Use of Medications and Services for the Management of Sickle Cell Disease

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Dedication

To my beloved family, my parents, Geeta and Rakesh, my brother, Prashant, my husband, Anshuman and my sweet dog, Zoi.

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Abstract

Use of Medications and Services for the Management of Sickle Cell Disease

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Sickle cell disease (SCD) is an inherited chronic disease with recurrent complications, high health care utilization and excessive costs. Preventative therapies, such as hydroxyurea, are known to prevent or reduce the frequency of SCD complications. The purpose of this study was to determine medication and healthcare services utilization for the management of SCD, in terms of index and subsequent therapies and services. This thesis also examined whether there were differences SCD-related prescription and healthcare utilization among patients of different age groups.

Texas Medicaid prescription and medical claims from September 1, 2011 to August 31, 2016 were retrospectively analyzed. Patients aged 2-63 years with a primary diagnosis of SCD (ICD-9: 282.6x, ICD-10: D57.1) and receiving one or more SCD-related medications (hydroxyurea, opioid or non-opioid analgesics) were included. The primary outcomes were type of SCD index drug, adherence to hydroxyurea, days' supply of opioid and non-opioid analgesics, utilization of SCD-related emergency department, inpatient and outpatient visits, and type of SCD index and subsequent healthcare services.

A total of 2,339 patients were included in the study. For the index drug, the majority of the patients were prescribed opioid analgesics (45.7%), followed by non-opioid analgesics (36.6%), and only 6.5 percent were prescribed hydroxyurea. Only 20.7 percent had a hydroxyurea medication possession ratio (MPR) ≥ 80%, with highest mean adherence among children. Days' supply of opioid and non-opioid analgesics was highest in older adults of age group 41-63. Healthcare service utilization was relatively high (compared to the general population) among age groups 2-12, 18-25 and 26-40. Slightly over one-third of the population (N=801; 34.3%) had either an index ED visit (74.7%) or ≥1 hospitalization (25.3%).

In conclusion, patients with SCD enrolled in Texas Medicaid have low utilization of and adherence to hydroxyurea. Interventions to increase its adoption and adherence could benefit patients by helping them better managing their SCD complications. Opioid use is prevalent among all patients with SCD, and generally, opioid use increased with increasing age groups. Patients with SCD also have a high use of healthcare services such as emergency department, inpatient and outpatient visits, especially among adolescents and young adults. Further research is needed to determine how to better manage patients with SCD, particularly adolescents and young adults who may be transitioning from pediatric to adult care.

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LIST OF ABBREVIATIONS

Acronym	Definition
ACIP	Advisory Committee on Immunization Practices
ACS	Acute chest syndrome
AHFS	American Hospital Formulary Service
ANOVA	Analysis of variance
APS	American Pain Society
ARE	Asymptotic relative efficiency
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD	Chronic kidney disease
CSSCD	Cooperative Study of Sickle Cell Disease
DVT	Deep vein thrombosis
ED	Emergency department
FDA	Food and Drug Administration
GCN No	Generic code sequencing number
Hb	Hemoglobin
HbA	Normal hemoglobin
HbF	Fetal hemoglobin
HbS	Sickled hemoglobin
HCUP	Healthcare Cost and Utilization Project
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
H/O	Hematologists/oncologists
HU	Hydroxyurea
ICD-9-CM	International Classification of Diseases, Ninth revision, Clinical Modification
MPR	Medication possession ratio
MSH	Multicenter Study of Hydroxyurea
MSOF	Multi-system organ failure
NGC	National Guideline Clearinghouse
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute of Health and Care Excellence
NIH	National Institutes of Health
NSAID	Nonsteroidal anti-inflammatory drug
PDC	Proportion of days covered
PE	Pulmonary embolism
PiSCES	Pain in Sickle Cell Epidemiology Study
QOL	Quality of life
RCT	Randomized controlled trail
SCA	Sickle Cell Anemia
SCD	Sickle Cell Disease

SCT	Sickle Cell Trait
TENS	Transcutaneous electrical nerve stimulation
US	United States
USPSTF	United States Preventive Services Task Force
VOC	Vaso-occlusive crisis

CHAPTER ONE: INTRODUCTION

Sickle cell disease (SCD) is defined as a group of genetically inherited chronic disorders characterized by a defect in the sickle cell hemoglobin (Hb) gene in red blood cells that imparts rigid, C-shaped, and sickle-like appearance to the red blood cells. This defect can be detected at the time of birth and it leads to several mild to severe complications throughout the life of affected individuals. Common complications of SCD include vaso-occlusive pain crises (VOC), acute chest syndrome (ACS), infections, leg ulcers, and anemia.[1] SCD and its complications are also associated with early mortality and shorter lifespan among patients with SCD as compared to the general population.[2]

A 2014 expert panel report from the National Heart, Lung, and Blood Institute (NHLBI) estimated that about two million people carry the sickle cell trait and around 100,000 people suffer from SCD in the United States (US).[3] Most of these people are of African descent, with one in every 365 African Americans suffering from SCD. Although less prevalent, SCD exists in people with Hispanic or Southern European, Middle Eastern, and Asian Indian ancestry.[4] Apart from premature deaths, SCD leads to a significant healthcare related financial burden due to frequent hospital admissions, emergency department visits, outpatient visits, and medication use. Kauf et al. estimated the total lifetime healthcare cost of about $1 million per person with SCD, and about 51 percent of this cost was specifically SCD-related.[5]

The severity of SCD varies among patients with different SCD genotypes. In the US, the distribution of SCD genotypes is as follows: about 75 percent of patients have genotype HbSS, 18 percent have HbSC, 4 percent have HbS/β^+-thalassemia, and about 2-3 percent have HbS/β^0-thalassemia.[6] While patients with HbSS/sickle-cell anemia disease and HbS/β^0-thalassemia have

severe to moderately severe complications, patients with HbSC disease and HbS/β^+-thalassemia have mild to moderately severe complications.[7]

SCD is associated with significant morbidity and mortality that adversely affect patients' quality of life. The most severe complications of SCD are initiated due to sickling of red blood cells followed by obstruction of capillaries and restriction of blood flow to organs. Patients have reported SCD-related pain (acute and/or chronic) on about 54.5 percent of patient-days, and they have utilized treatment for pain on 3.5 percent of patient-days.[8] Furthermore, restriction of blood flow leads to venous incompetence, anemia, bacterial infections, trauma, inflammation, and ulceration in the extremities (e.g., legs, ankles, fingers and toes).[9] One study suggested that nearly 25 percent of patients reported a history of leg ulcers, suffered active ulcers at entry, or developed ulcers during the eight years of the study period.[10] Patients with SCD also suffer from pulmonary complications called acute chest syndrome (ACS) which is also the leading cause of mortality in patients with SCD.[11]

Although SCD leads to significant complications and cost burden, few drug therapies exist for its management. Hydroxyurea (HU) was the first, and until recently, the only drug approved for the indication of SCD. It is also the most readily available and affordable drug used in SCD management. NHLBI guidelines have specific recommendations for HU therapy among patients with SCD by age groups. HU therapy is recommended among children up to 12 years and adolescents (13-17 years) regardless of SCD clinical severity. Moreover, HU therapy is strongly recommended among adults (≥18 years) experiencing three of more vaso-occlusive crisis (VOC) events per year, severe and/or recurrent ACS, and severe symptomatic chronic anemia and pain. While HU is well-known to reduce the frequency and severity of SCD-related complications, mainly VOC pain and ACS, its uptake has been limited. There has been limited research on the

reasons associated with underutilization of HU. Barriers related to low uptake of HU include physicians' concerns of carcinogenic potential, uncertainty about effectiveness, perceived patient apprehension about adverse effects, concerns about lack of contraceptive use and patient adherence.[12] Reversible cytopenia and bone marrow suppression are the most common side effects of HU use.[3, 13]

Other drugs commonly used to manage complications of SCD, mainly acute and chronic pain, include opioid and non-opioid analgesics. While non-opioid analgesics are recommended for mild pain, weak opioids are used for moderate pain and strong opioids are used for severe pain. Often times, non-opioid analgesics are given as adjuvant therapy to limit the use of parenteral opioids. Both opioid and non-opioid analgesics are accompanied with side effects; non-opioids could lead to high blood pressure and reduced kidney function, while opioids cause more severe side effects such as sedation, respiratory depression, tolerance, and addiction. As opioid use is highly prevalent among patients with SCD, providers are concerned about the potential abuse of these drugs in this patient population. However, it has also been noted that providers often overestimate opioid dependence in these patients and fail to prescribe opioids appropriately. This results in the undertreatment of SCD-related pain in many patients.[14, 15, 16, 17]

Moreover, some other drugs such as folic acid, antibiotics, decitabine, and Endari® are also used in SCD management. Folic acid acts as a supplement by replenishing depleted folate levels caused by high red blood cell turnover in patients with SCD. A sufficient amount of folate in the body is essential for the production of red blood cells.[18] Patients with SCD, especially infants and children five years and less, are prone to bacterial infections that, in some cases, could be fatal. Antibiotics such as penicillin, amoxicillin, cefuroxime, and clarithromycin are used for the treatment and prophylaxis against these infections.[1] Decitabine, a drug indicated for treatment of

adult patients with myelodysplastic syndromes, is used off-label for SCD and has been known to significantly increase the level of fetal and total hemoglobin and improve clinical end-points in patients with severe and recurrent sickle cell anemia.[19] Finally, in July 2017, Endari®, an L-glutamine oral powder was approved by the United States Food and Drug Administration (US FDA) for the management of acute SCD complications for patients five years and older.[20]

Despite improvements in SCD care, the NHLBI report identified several gaps in the management of SCD and its complications.[3] Savage et al. summarized these gaps in care and listed areas that need further exploration such as studies with opioids in combination with non-opioid drugs to assess overall opioid utilization, frequency of emergency department or hospital visits, and longitudinal studies of outcomes and safety of SCD management that includes long-term opioid safety, impact of HU therapy on analgesic use and overall healthcare utilization.[21]

While effectiveness of individual therapies has been established and guidelines recommend use of various drugs to manage SCD complications, evidence is lacking on how these medications are used holistically in SCD management. Research is needed to explore how patients are managing their SCD complications in the real world. Do patients with SCD seek drug therapies and medical care reactively following a trigger event (VOC, ACS, leg ulcers or stroke)? Are they adherent and persistent with the drugs prescribed by providers as per guidelines? As guidelines for medication use (HU and opioid analgesics) differ based on age groups of patients with SCD, it seems pertinent to explore real-world medication utilization, especially for HU and opioid analgesics, by age groups. There is a need to study the medication use patterns to understand whether therapies differ among patients with SCD of various age groups. Additionally, it is essential to understand the healthcare utilization patterns in SCD management among patients of different age groups to identify gaps in care and where interventions may be needed.

The purpose of this proposed study is to explore the temporal use of medications for the management of sickle cell disease in terms of index and subsequent therapies and determine whether there are differences in prescription drug use and SCD-related healthcare utilization among patients with SCD of different age groups.

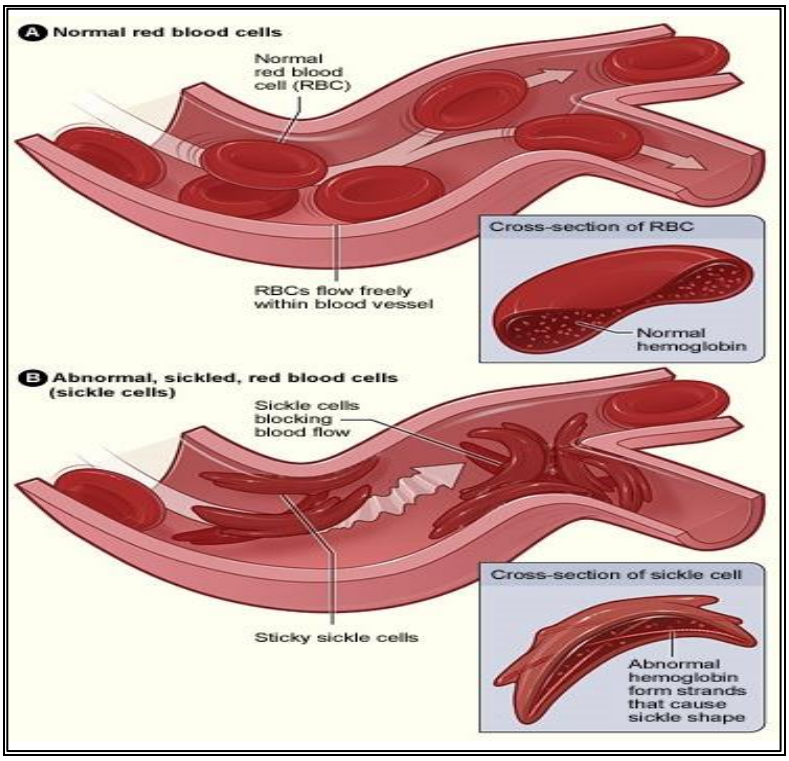
CHAPTER TWO: LITERATURE REVIEW

The literature review covers the following topics as they relate to SCD: disease overview, prevalence, incidence, morbidity and mortality statistics, economic burden of SCD, distribution of SCD genotypes in US patients, complications associated with SCD (vaso-occlusive crisis(VOC), acute chest syndrome (ACS), leg ulcers), and various guidelines for SCD management. Other topics covered include types of medications used in SCD management, their mechanism of action, side effects, information available on the use of these medications, and healthcare utilization among patients with SCD.

2.1 Sickle Cell Disease Overview

Sickle cell disease is a genetically inherited group of disorders that affects the red blood cells of the circulatory system. It is characterized by the presence of abnormal hemoglobin in the red blood cells that leads to hardened, stiffened, C-shaped, 'sickle-like' or 'crescent-like' red blood cells. Healthy red blood cells, being round and doughnut-like, are flexible to drift smoothly through large and small blood vessels in the circulatory system; however, sickle-shaped cells become elongated, hard and they stick to the walls of the small blood vessels. This leads to blockage within the blood vessels, slowing or ceasing blood flow and hence, limiting the oxygen supply to the nearby tissues. This further leads to other complications such as acute pain, infections, fever, anemia, ACS and leg ulcers.[1,4] Figure 2.1 depicts how sickled red blood cells differ from normal red blood cells.

Figure 2.1 Normal Red Blood Cell vs Sickled Red Blood Cell



[1] Adopted from National Heart, Lung, and Blood Institute. National Institutes of Health. U.S. Department of Health & Human Services. What Is Sickle Cell Disease?

2.2 Prevalence and Incidence

Sickle cell disease is not contagious, but it is genetically inherited from parents to their children. Every newborn in the US undergoes a simple blood test at the time of birth to allow early diagnosis of SCD.[1] Estimates from the Centers for Disease Control and Prevention (CDC) suggest that around two million people carry the SCD gene in the US, of which around 100,000 people suffer from SCD. Most of these people are of African descent, with one in every 365 African Americans suffering from SCD. Furthermore, about one in thirteen African American babies is born with a sickle cell trait (SCT).[4] The disease is also prevalent in people with Hispanic, southern European, Middle Eastern and Asian Indian ancestry, but to a lesser extent.[3]

2.3 Mortality Statistics

A review by Diggs in 1973 estimated a median lifespan of about 14 years for patients with SCD with most people dying by 30 years of age.[22] With advancement in the early diagnosis and medical care over the years, there has been significant improvement in the lifespan of patients with SCD. While life expectancy of most patients with SCD currently ranges from 40-60 years, their average lifespan is still 20-30 years shorter than the general population, which indicates premature mortality.[2]

2.4 Economic Burden of SCD

Apart from premature deaths among children and adults, SCD also leads to a significant healthcare related financial burden in the US. A 2009 study by Kauf et al. estimated the total lifetime healthcare cost to be $1 million per person with SCD, with annual costs ranging from $10,000 for children to $30,000 for adults. The study also found that about 51 percent of these costs (including emergency department visits, inpatient hospitalizations, and prescription drugs) were specifically SCD-related costs.[5]

2.5 Distribution of Sickle Cell Disease Genotypes in US Patients

SCD is caused by the presence of homozygous genes for a single amino acid mutation in the β-globin chain resulting in abnormal hemoglobin S, or the presence of heterozygous hemoglobin S with another abnormal β-globin chain, such as hemoglobin C or β-thalassemia. Initially developed among people living in areas prone to malarial infections, the sickle cell trait originated in geographical regions of sub-Saharan Africa, the Middle East, and the Indian subcontinent (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka). In subsequent years, the gene spread to other parts of the world including the US and European countries due to

human migration. The sickle gene evolved to provide people with a genetic advantage against the malarial parasite, *Plasmodium falciparum*, which prevents malarial infections in heterozygous carriers. However, it leads to several complications in homozygous sickle cell patients.[6, 7]

Individuals who inherit one sickle gene and one normal gene have the sickle cell trait (SCT). Though these people remain asymptomatic throughout their lives, they can pass on the disease to their children. Children born to both parents with the sickle cell trait have a 25 percent chance of being born with SCD, a 50 percent chance of having the SCT, and a 25 percent chance of not having either of those (inheriting normal genes).[4] In patients with SCD, upon deoxygenation, hemoglobin S polymerizes imparting rigidity to the sickle blood cells, which in turn, leads to a sickling and early destruction of these cells. Other SCD manifestations, include: vaso-occlusion, vaso-occlusive pain crises, bone marrow ischemia, hemolysis, hemolytic anemia, ACS, pulmonary hypertension, leg ulcers, priapism, strokes, and organ damage within the spleen, kidneys, liver and bones.[6]

In the US, the most commonly found SCD genotypes are HbSS, HbSC, HbS/β^+-thalassemia and HbS/β^0-thalassemia. Hemoglobin SD (HbSD) and hemoglobin SE (HbSE) are other rare genotypes, mainly seen in Indian and Arab populations and are not common in the US. While most patients with genotype HbSE largely remain asymptomatic, patients with genotype HbSD present with mild to moderate clinical complications.[23, 24] Data obtained from more than 1,500 patients with SCD enrolled in three large multi-center studies conducted in the US, the UK and Brazil[25] illustrates the distribution of predominant SCD genotypes in African origin patients in the Americas and the UK. Specifically, for the US, data estimated that about 75 percent of patients had genotype HbSS, 18 percent had HbSC, 4 percent had HbS/β^+-thalassemia, and less than 2 percent had HbS/β^0-thalassemia. Table 2.1 summarizes the distribution of SCD genotypes

in the US and the UK as observed from the patient data obtained from the two main studies (US-PUSH and US, UK-walk-PHaSST).[7, 26, 27]

Table 2.1 Distribution of Sickle Cell Disease Genotypes in the US and UK

	Children and adolescents (US-PUSH) N= 504	**Adolescents and adults (US, UK-walk-PHaSST) N=674**
Hemoglobin SS (HbSS)	75.6%	74.9%
Hemoglobin SC (HbSC)	17.8%	18.1%
Hemoglobin S/β^+-thalassemia (HbS/β^+-thalassemia)	3.6%	4.0%
Hemoglobin S/β^0-thalassemia (HbS/β^0-thalassemia)	1.8%	1.6%
Other	1.2%	1.4%

US- United States
UK- United Kingdom
PUSH- Pulmonary Hypertension and the Hypoxic Response in SCD
PHaSST- Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy
[7] Recreated using data from Saraf SL, Molokie RE, Nouraie M, Sable CA, Luchtman-Jones L, Ensing GJ, Campbell AD, Rana SR, Niu XM, Machado RF, Gladwin MT. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatric Respiratory Reviews. 2014 Mar 1;15(1):4-12.

Patients with different SCD genotypes experience considerably different levels of severity with respect to the SCD complications. Some patients with SCD remain asymptomatic for most of their lives, while others suffer severe and frequent complications leading to premature mortality. The variations in severity and frequency of SCD complications are based on the different rates at which the deoxygenated hemoglobin sickle cells polymerize. At a more fundamental level, intraerythrocytic HbS concentration, degree of cell deoxygenation, pH, and the intracellular

concentration of HbF affect the polymerization rates of sickle cells.[6, 28] Table 2.2 summarizes the level of severity among the predominant SCD genotypes found in the US patient population. The manifestation of specific SCD complications among different genotypes will be discussed in subsequent sections.

Table 2.2 Severity of Sickle Cell Disease Complications in Different Genotypes

Sickle-cell disease genotypes	**Severity of disease**
HbSS disease or sickle-cell anemia	Usually a severe or moderately severe phenotype
HbS/β^0-thalassemia	Usually a severe or moderately severe phenotype
HbSC disease	Intermediate severity
HbS/β^+-thalassemia	Mild to moderate severity; varies in different ethnic groups
HbS/hereditary persistence of fetal Hb	Very mild and mostly symptom-free
HbS/HbE syndrome	Very rare and generally very mild clinical course

Hb- Hemoglobin
[6] Adapted from Stuart MJ, Nagel RL. Sickle-cell disease. The Lancet. 2004 Oct 9;364(9442):1343-60.

2.6 Complications of SCD

Even though SCD is diagnosed at the time of birth, the initial signs and symptoms do not appear until the infant is four to five months old because the presence of fetal hemoglobin (HbF) in newborns prevents the sickling of red blood cells. As the infant grows, fetal hemoglobin is replaced by sickle hemoglobin which causes sickling of the red blood cells.[29] SCD leads to several complications throughout the life of a person including hand-foot syndrome (swelling, pain and blisters in hands and feet), pain due to VOC, sickle cell anemia, bacterial infections, ACS, splenic sequestration, vision loss, leg ulcers, stroke, deep vein thrombosis (DVT) and pulmonary

embolism (PE), priapism, and damage to the organs. Most of these complications lead patients to the emergency department (ED), which is often followed by an inpatient hospitalization.[3, 4] Three of the most common complications, VOC, ACS, and leg ulcers are discussed in detail below.

2.6.1 Vaso-Occlusive Crisis

Vaso-occlusive crisis (VOC) is the most common complication of SCD in children and adults. It is also the primary reason for emergency department visits, hospitalizations and healthcare utilization among these patients. It is initiated due to obstruction of capillaries and restriction of blood flow to organs caused by sickled red blood cells which leads to ischemic tissue injury. VOCs can lead to other serious complications such as pain syndromes, leg ulcers, renal insufficiency, stroke and spontaneous abortion. With time, recurrent VOCs can result in chronic pain due to destruction of bones, joints and visceral organs. Unpredictable occurrences of acute pain coupled with chronic pain creates a pain syndrome that remains incompletely treated in many cases. While most cases of VOC resolve within five to seven days, severe cases may persist for weeks or months.[30, 31]

A longitudinal, prospective US study conducted by Platt et al. using data from 1979-1988 studied the rate and risk factors associated with VOC among 3,578 patients with SCD aged 0 to 66 years. The study found varying rates in the number of VOC episodes among patients with SCD with different genotypes. In the overall study cohort, about 39 percent of patients had no pain episodes over a year, while patients with sickle β^0-thalassemia had three to ten pain episodes per year. They also found that the clinical severity of the VOC was positively correlated to premature deaths in patients with SCD, and the presence of fetal hemoglobin in the blood can lower the pain rate and improve survival.[8] Another study by Smith et al. assessed daily pain in adults suffering from SCD. This prospective study examined the prevalence of VOC pain as self-reported by the

patients, and evaluated the relationship between pain severity, crisis and utilization. The self-reported pain diaries revealed that pain occurred on 54.5 percent of patient-days, but treatment utilization occurred on only 3.5 percent of patient-days.[9] Vaso-occlusive pain is managed using various methods including pharmacotherapy with drugs such as opioid and non-opioid analgesics. These methods are discussed in detail in later sections.

2.6.2 Acute Chest Syndrome (ACS)

Another common complication of SCD is acute chest syndrome (ACS), which is a pulmonary complication. ACS is the leading cause of mortality in patients with SCD and it ranks as the second most common reason for SCD-related hospitalizations. It is a pneumonia-like illness characterized by fever, cough, sputum production, shortness of breath, retractions, rales, dyspnea, or hypoxia. Often times, VOC is followed by an ACS event. The most common causes of ACS are pathogenic infections and pulmonary embolism; however, in some cases, the cause remains unclear due to lack of distinctive laboratory features of ACS.[32]

In 2000, Vichinsky et al. conducted a multicenter study analyzing 671 episodes of ACS in 538 patients with SCD to determine the cause and outcomes of ACS events. Among the study population, the mean length of hospitalization was 10.5 (SD not provided) (Range- 9.7- 12.8) days. Pulmonary fat embolism and various pathogenic infections were identified as causes of ACS events in 38 percent of ACS episodes. These two factors also caused the majority of deaths, with infection being a contributing factor in 56 percent of deaths.[33] An older study by Poncz et al. prospectively analyzed 102 episodes of ACS in hospitalized patients over a period of two years to evaluate the causes and clinical correlates of ACS. Findings suggested that about 12 percent of the ACS episodes occurred after bacterial pneumonia, 8 percent were related to viral pneumonias, and 16 percent were associated with mycoplasmal pneumonias. The etiology behind the remaining 64

percent of episodes remained unclear. Researchers also found that when compared to patients with undetermined ACS origin, the patients suffering from bacterial pneumonias which led to ACS were sicker, required longer hospitalizations, and a larger proportion of these patients received red blood cell transfusions.[32]

Furthermore, studies have been conducted to determine the frequency, severity, and overall impact of ACS. A nationwide Cooperative Study of Sickle Cell Disease (CSSCD) was a national collaborative program launched in the US in 1977. The program observed more than 3,000 patients with SCD in order to study the natural history of SCD and the risk factors leading to SCD-related mortality and morbidity. Using the data obtained from this program, a study was conducted among 3,751 patients with SCD from March 1979 to September 1988 to evaluate the incidence and risk factors associated with ACS. The researchers observed a total of 19,867 patient-years. During the study period, 1,085 patients with SCD suffered a total of 2,100 ACS episodes. While most patients (~55%) only suffered one ACS event, some suffered multiple ACS events. Incidence rates of ACS varied significantly among patients by age group and genotype. Incidence rates of ACS were higher among children aged 2 to 4 years as compared to infants aged less than 2 years (21.5 to 25.8/100 patient-years, respectively), and the higher incidence was attributed to lower concentration of HbF in children 2 to 4 years of age. Additionally, to determine if ACS was linked with higher mortality, the study compared survival between patients who had at least one ACS event within the first two years of follow-up to patients who did not have any ACS events during the same period. Analysis suggested that having at least one ACS event was significantly associated with lower survival ($p=0.043$).[11]

Generally, ACS subsides after a few days of hospitalization and treatment with broad spectrum antibiotics. But in severe cases, patients can develop respiratory failure and/or

complications in other organs such as the brain, liver, and kidneys, which can then lead to multisystem organ failure (MSOF). In a study by Vichinsky et al., treatment protocols using techniques such as matched transfusions, bronchodilators, bronchoscopy, and mechanical ventilation led to clinical improvement and recovery in ACS patients.[33]

2.6.3 Leg Ulcers

Leg ulcerations are another common and often disabling complication of SCD. Chronic leg ulcers were observed and recognized as a complication in some of the earliest cases of SCD studied in the US.[34] Researchers proposed that leg ulcers occur due to obstruction of sickled cells, excessive vasoconstriction, venous incompetence, narrowing of endothelial walls due to decreased nitric oxide bioavailability, and sickle cell anemia. All these factors restrict the supply of oxygen to the tissues in the extremities, hence causing bacterial infections, trauma, inflammation, and ulcerations. These ulcers are predominant in areas with thin skin, less subcutaneous fat and reduced blood supply such as the ankles.[35]

To examine the frequency of leg ulcers in patients with SCD, Koshy et al. conducted a study using data from patients who enrolled in the CSSCD program between 1979 and 1986. Overall, about 25 percent of patients reported a history of leg ulcers, suffered active ulcers at entry, or developed ulcers during the eight year study period. They also found that the frequency of occurrence of leg ulcers was higher among sickle cell anemic HbSS genotype (9.97/100 patients) and HbSS α-thalassemia genotype (5.70/100 patients). On the contrary, it was noted that patients with HbSβ^+ thalassemia and HbSC genotypes did not suffer from leg ulcers. Other risk factors related to higher frequency of leg ulcers were gender, age, levels of total Hb, HbF, and α-gene deletion. Males (15/100 men) were more likely to have leg ulcers than females (5/100 women). Incidence rates of ulcers increased significantly with age. In the 10- to 19-years age group, the

incidence rate of ulcers was 0.671/100 person-years, while it increased substantially and ranged from 7.57 to 19.17 per 100 person-years among patients older than 20 years of age. Additionally, lower levels of Hb and HbF and lower frequency of α-gene deletion were linked to higher incidence rates of leg ulcers.[3, 10, 36]

SCD-related leg ulcers vary in size from a few millimeters in diameter to large ulcers involving the entire distal lower extremity. They appear round and punched-out with raised margins and deep bases containing necrotic material. They are also surrounded by dark and hardened skin, and sometimes penetrate to the muscles and underlying bone. The onset of these ulcers could be triggered by minor trauma, insect bites, scratching, or from blood draws or intravenous therapy. Oftentimes, these ulcers are worsened by secondary bacterial infections that further impede healing. The ulcers are accompanied by sharp, severe, stinging, and unremitting pain, leading to significant disability among patients.[35, 37]

Because of the adverse impact of leg ulcers, studies have been conducted that specifically focus on disability and repercussions on quality of life associated with leg ulcers among patients with SCD. A French referral center for SCD followed 20 patients who had previous/active leg ulcers. The median time covered with ulcerated skin was 29.5 months, ankle stiffness was observed in 50 percent, and mood disorders were observed in 85 percent of patients. About 90 percent of patients used analgesics to manage the associated pain, of which 20 percent were opioid analgesics. Some patients suffered severe, prolonged ulcers that recurred frequently and were further associated with priapism, pulmonary hypertension, stroke, and ACS. These patients reported poor quality of life (QOL) which was measured by the Short Form 36 Health Survey, with mean scores of 41.5 for the physical component and 40.7 for the mental component. These QOL scores were similar to lung cancer and hemodialysis patients.[38]

Moreover, it is important to note that SCD-related leg ulcers are more severe, frequent, and painful than most other lower extremity wounds. They heal at a significantly lower rate, and patients take months or even years to recover from these ulcers. Topical, systemic and surgical interventions are used to manage and treat these ulcers. Topical antibiotics such as neomycin, polymyxin B, and bacitracin are used to treat infection associated with the ulcers. Topical analgesics (opioids and non-opioids) are used to control associated pain. [39, 40]

2.7 National Guidelines for Sickle Cell Disease Management

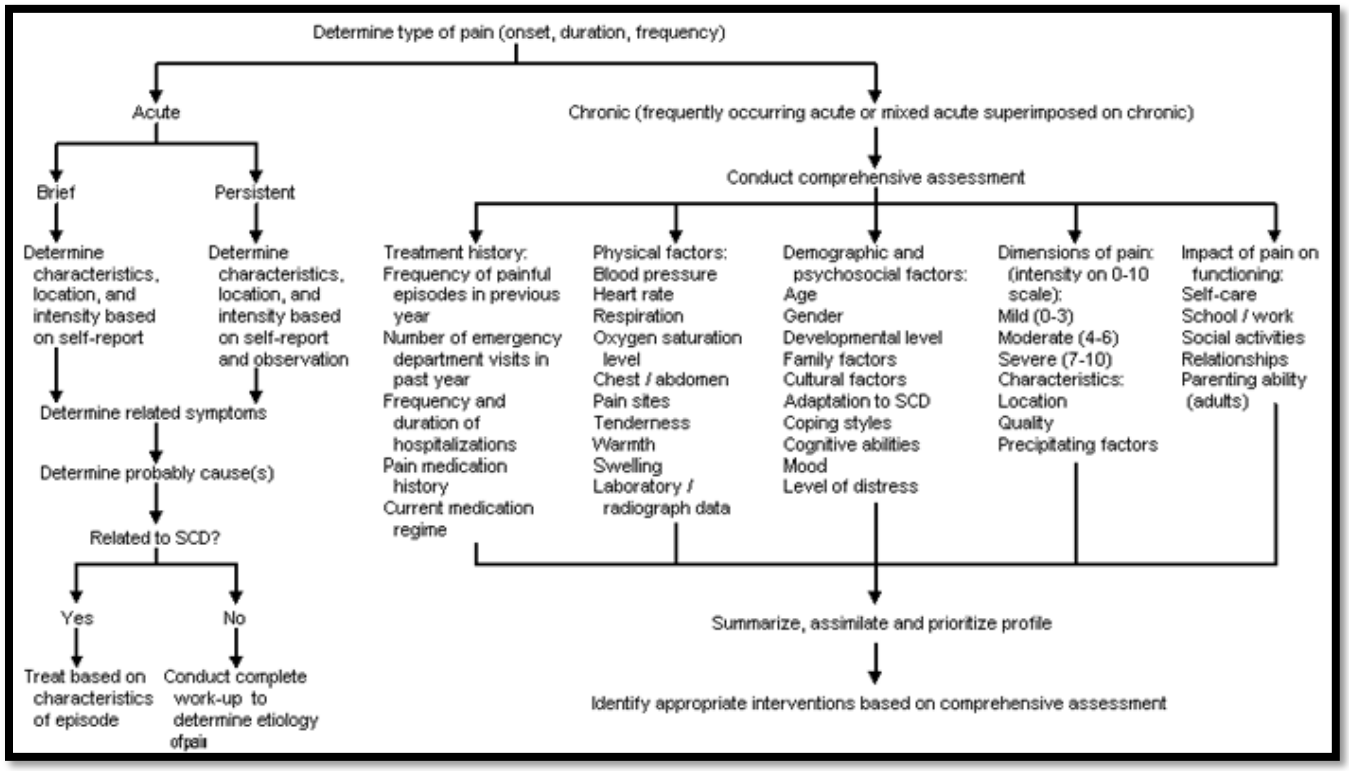
Overtime, agencies in the US and the UK have developed guidelines for the management of SCD, mainly for VOC. While most guidelines only provide recommendations regarding management of SCD-related pain (acute and/or chronic), the NHLBI guidelines also include extensive recommendations to assist healthcare providers, patients and their caretakers in managing SCD and its various complications. The guidelines include recommendations regarding routine health maintenance, recognition and treatment of common acute and chronic complications of SCD, hydroxyurea (HU) indication and monitoring, and blood transfusion therapy. The most utilized guidelines are reviewed in the following sections.

2.7.1 American Pain Society Guideline

The American Pain Society (APS) released the first evidence-based guideline for the management of acute and chronic SCD-related pain in the US in August 1999. The guideline was developed utilizing a systematic review of scientific evidence and expert judgment. The recommendations of this guideline were used as a reference during the development of the NHLBI SCD guidelines for the management of acute pain crises.[41] Specifically, this guideline includes a

detailed flow chart for physicians for pain assessment (Figure 2.2).[42] However, this guideline does not include recommendations for the managing chronic complications associated with SCD, use of HU for SCD, blood transfusion, and general health maintenance among the SCD patient population.

Figure 2.2 Flow Chart for Sickle Cell Pain Assessment



SCD- Sickle Cell Disease

[43]Adopted from Benjamin LJ, Dampier CD, Jacox A, Odesina V, Phoenix D, Shapiro B, Strafford M, Treadwell M. Guideline for the management of acute and chronic pain in sickle cell disease. Glenview, IL: American Pain Society. 1999.

2.7.2 National Heart, Lung, and Blood Institute Guidelines

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the National Guideline Clearinghouse (NGC), provides recommendations to assist healthcare professionals in evidence-based management of SCD. This guideline, published in 2014, will be discussed in detail

as it is the most recent and comprehensive of all the guidelines on SCD management. The guideline is comprised of five main topics that cover different aspects of SCD management: management of acute complications, management of chronic complications, HU therapy, blood transfusion therapy, and health maintenance of patients with SCD. The specific guideline topics are described further below.

2.7.2.1 Management of acute SCD-related complications

Acute complications associated with SCD include VOC, fever, acute renal failure, priapism, hepatobiliary complications, acute anemia, splenic sequestration, ACS, acute stroke, multisystem organ failure (MSOF), and acute ocular conditions.

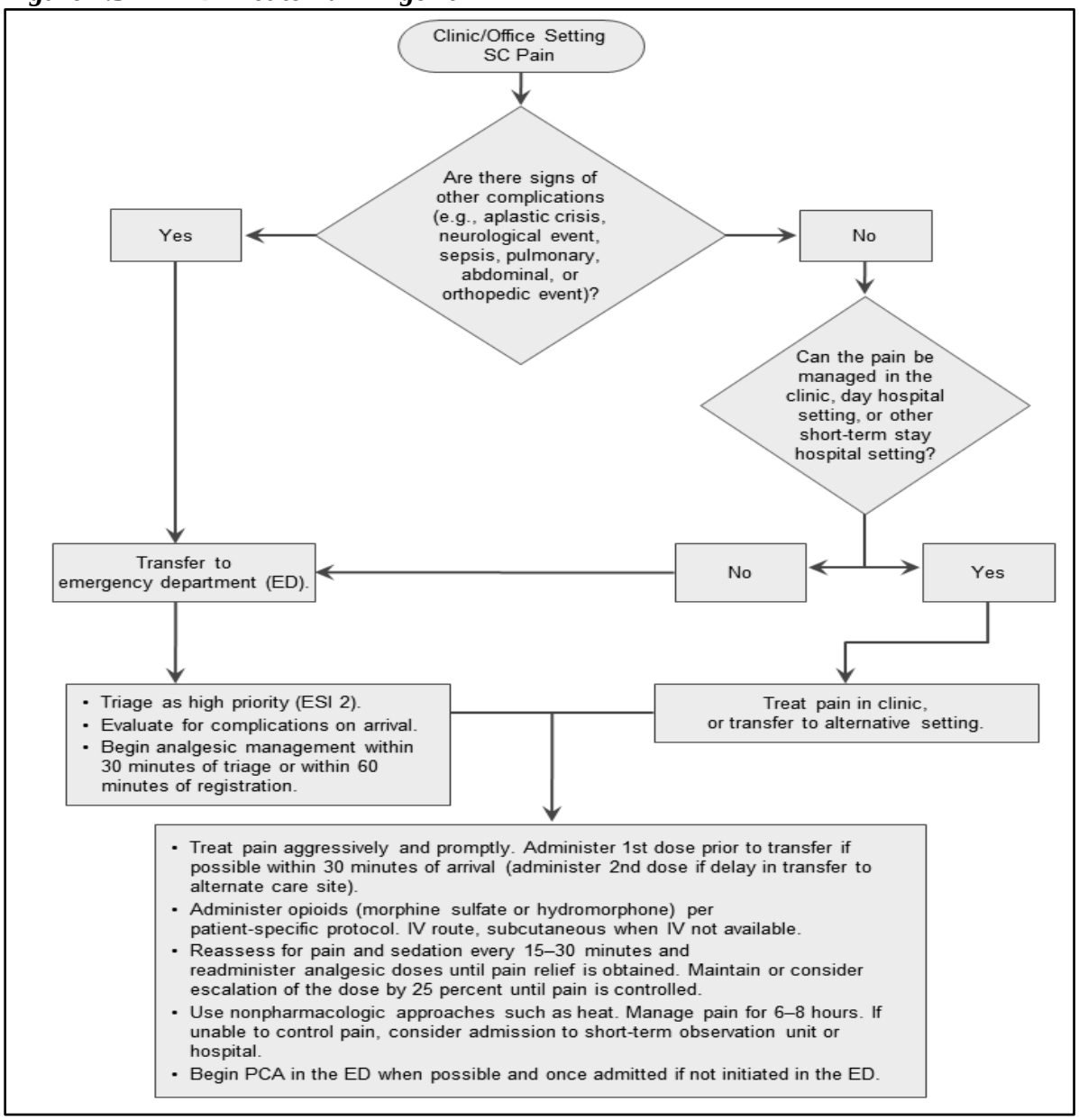
The most common complication associated with SCD that leads to ED visits and/or hospitalization is VOC. Vaso-occlusive crises are characterized by periodic episodes of excruciating musculoskeletal pain caused by adhesion of sickle cells to the walls of blood vessels resulting in reduced blood flow to various body parts.[44] These painful crises, commonly occurring in the extremities, chest and back, range from mild to severe, and lead to significant morbidity among patients with SCD.[8] In most cases, mild and moderate pain episodes can be alleviated at home using hydration, heating pads, massage, and mild non-opioid analgesics (acetaminophen, ibuprofen). However, more severe pain episodes require hospitalization.[45]

The NHLBI 2014 expert panel report presents recommendations for acute management of vaso-occlusive crises, with some recommendations based on evidence from the literature, and others adopted from the American Pain Society or from expert panels. According to the report, the following steps should be taken by healthcare providers during a VOC crisis in a patient (children and adults):[3]

a) Assessment of the etiology of pain to rule out any causes other than a VOC.
b) Determination of the characteristics, symptoms, location, and intensity of pain by observation and as self-reported by the patient. Furthermore, the patient's recent analgesic use (opioid and non-opioid) should be assessed.[46]
c) In patients (children and adults) with mild to moderate pain who report relief with nonsteroidal anti-inflammatory drugs (NSAIDS) without any contraindications, treatment should be continued with NSAIDS.
d) In cases of severe VOC pain in children and adults, treatment with parenteral opioids should be initiated rapidly. Selection of the opioid and its dose should be done by assessing the symptoms, outpatient analgesic use, patients' past experience with side effects and knowledge of effective agents and doses.
e) In some cases, as per requirement, oral adjuvant NSAIDS or antihistamines are prescribed to control pain and secondary itching, respectively.[3]

The flow chart below outlines the recommendations for the management of acute VOC pain crisis in a clinical setting as per the NHLBI guidelines report (Figure 2.3).

Figure 2.3 NHLBI Acute Pain Algorithm



SC- Sickle Cell, ED- Emergency Department, ESI- Emergency Severity Index, IV- Intravenous, PCA- Patient-Controlled Analgesia

[3] Adapted from National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014.

2.7.2.2 Management of chronic SCD-related complications

Chronic complications associated with SCD include chronic pain, avascular necrosis, leg ulcers, pulmonary hypertension, renal complications including various stages of chronic kidney disease (CKD) to kidney failure, recurrent priapism, and chronic ophthalmologic complications.[3]

The most common chronic complication of SCD is chronic pain which is defined as pain that lasts more than three months. SCD-related chronic pain can be nociceptive pain, i.e., initially arising from external stimuli such as sports injury, a dental procedure, or arthritis, or neuropathic pain, i.e., resulting from injury, damage or disease affecting the nervous system. The Pain in Sickle Cell Epidemiology Study (PiSCES) found that adults (N=232) reported pain at home during 55 percent of the total 31,017 days surveyed.[9] Similarly, children (N=39) reported pain at home during 8.4 percent of the total 1,515 days surveyed.[46] Medications such as NSAIDs, opioids, antidepressants and anticonvulsants are used for chronic pain management. Providers' primary aims when managing SCD-related chronic pain are to restore function and improve quality of life, while minimizing opioid risk, abuse, misuse or diversion. Nonpharmacological approaches including psychological intervention, occupational therapy, behavioral and cognitive interventions, acupuncture, mild to moderate exercise, and aquatic therapy are also used to manage chronic pain.

The NHLBI 2014 expert panel developed recommendations for SCD-related chronic pain management based on findings and evidence from randomized controlled trials, observational studies, case reports, and guidelines for the management of chronic pain published by the American Pain Society in collaboration with the American Academy of Pain Medicine. According to the report, the following should be considered by healthcare providers while developing a management plan for chronic pain in patients with SCD:[3]

a) Determine the cause and type of SCD-related chronic pain by using signs and symptoms such as avascular necrosis, leg ulcers, or pain due to neuroplasticity of the peripheral or central nervous system. The assessment includes descriptors of the pain, severity on a numerical scale, location of the pain, factors that aggravate or alleviate it, and its effect on patient's mood, activity, employment, quality of life and vital signs.
b) Patients are encouraged to use deep tissue or deep pressure massage therapy, muscle relaxation therapy and self-hypnosis.
c) Long- and short-acting opioids are used to manage pain not relieved by non-opioids.
d) An individualized treatment plan for long-term opioid use is developed based on the patient-reported effectiveness of prior use of opioids, their response to treatment, pain relief, side effects and functional outcomes.
e) Biweekly or monthly opioid prescriptions are written, and chronic opioid therapy is evaluated in each patient every 2-3 months to minimize tolerance and abuse of opioids.
f) Patients are referred to a mental health professional such a psychiatrist, social worker, or addiction specialist as needed.

In addition, providers must check patients with SCD for leg ulcers as they are a common complication among these patients. Providers are recommended to conduct physical examination of lower extremities to identify any active or healed ulcers, number of ulcers as well as severity and depth. While less severe leg ulcers can be treated with initial standard therapy constituting of debridement, wet to dry dressings, and topical agents, chronic/persistent/ deep/recalcitrant ulcers must be treated by a wound care specialist or multidisciplinary wound team. Systemic or local antibiotics are used if the ulcers are infected.[3]

2.7.2.3 Hydroxyurea therapy in SCD management

Hydroxyurea (HU), also known as hydroxycarbamide, has been used in adults and children suffering from SCD to reduce the frequency and severity of SCD-related acute and chronic pain, as well as the incidence of ACS. The NHLBI 2014 expert panel developed recommendations for HU therapy for SCD management primarily based on systematic review findings of three randomized controlled trials. However, findings and evidence from several observational studies and studies conducted among different patient populations, including pediatric populations, were also incorporated. Of note, HU therapy guidelines differ based on age groups. According to the expert panel report, the following steps should be taken by healthcare providers while considering treatment with HU for the management of patients with SCD:[3]

a) All patients with sickle cell anemia (SCA) must be educated regarding HU therapy.
b) HU should be specifically prescribed to the following adult patients:
    i. Adults with SCA who experience three or more VOCs in a 12-month period,
    ii. Adults with SCA who have a history of severe and/or recurrent acute chest syndrome, and
    iii. Adults with SCA who have severe symptomatic chronic anemia or SCD-related pain that interferes with their daily activities and quality of life.
c) Based on high-quality evidence among children with SCA aged 9-42 months and moderate-quality evidence among children aged >42 months and adolescents with SCA, the panel strongly recommended use of HU among these patient populations to reduce SCD-related complications, such as pain, ACS anemia and dactylitis (i.e., swelling of fingers and toes).

d) HU therapy can improve anemia in adults and children with SCD who have chronic kidney disease and take erythropoietin.
e) HU therapy should also be considered in people with HbS/β+-thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life.
f) HU should be discontinued in pregnant and breastfeeding women due to teratogenic effects.[3]

Figure 2.4 shows a prescribing and monitoring protocol that should be followed to ensure proper use of HU and maximize its benefits and safety.

Figure 2.4 Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- **Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease**
- **Starting dosage for infants and children: 20 mg/kg/day**
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count ≥2,000/uL; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/uL.
- Maintain platelet count ≥80,000/uL
- If neutropenia or thrombocytopenia occurs:
  - Hold hydroxyurea dosing
  - Monitor CBC with WBC differential weekly
  - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
  - Increase by 5 mg/kg/day increments every 8 weeks
  - Give until mild myelosuppression (absolute neutrophil count 2,000/uL to 4,000/uL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
  - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6- month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
  - Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

[3] Adopted from National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014.

2.7.2.4 Blood transfusion in the management of SCD

Blood transfusion, also known as donor erythrocyte (red blood cell) transfusion, is an important therapy in SCD management as it targets the pathophysiology of SCD. It involves transfusion of donor erythrocytes containing normal hemoglobin (HbA) into patients with SCD to reduce the percentage of circulating erythrocytes containing abnormal hemoglobin (HbS). This therapy not only ameliorates many acute and chronic complications associated with SCD, but also prevents SCD manifestations in some patients. While blood transfusion has several benefits in patients with SCD, it is also associated with side effects, such as alloimmunization (immune response to foreign antigens), autoimmunization (immune response against own cells), iron overload (excessive iron in the body), hyperviscosity (increased viscosity of blood), and hemolysis (rupture/destruction of erythrocytes).[47, 48, 49]

Donor erythrocytes can be administered using two methods: *a) simple transfusion, and b) exchange transfusion*. In simple transfusion, donor erythrocytes are infused in the recipient's body without removal of their blood. In exchange transfusion, recipient's blood is removed before and/or during the donor erythrocyte infusion. Exchange transfusion has important benefits over simple transfusion, which are as follows:

i. It increases the percentage of red blood cells containing normal hemoglobin.
ii. It allows transfusion of increased volumes of donor blood without increasing the hematocrit levels, hence preventing hyperviscosity.
iii. It reduces the net transfused volume, hence preventing iron overload.

However, there are certain risks of exchange transfusion which include increased donor erythrocyte exposure and higher risk of subsequent alloimmunization, higher costs, need for more sophisticated equipment, and frequent need for permanent venous access.[3]

Blood transfusion has three main indications among patients with SCD which are as follows:

a) *Prophylactic use*- This episodic blood transfusion is administered prophylactically prior to anesthesia or surgery. As surgeries can cause significant morbidity among individuals with SCD (12 deaths in 1,079 surgical cases),[50] prophylactic transfusions are used during perioperative periods to prevent SCD-related complications such as VOCs, ACS, or stroke. NHLBI guidelines on prophylactic blood transfusion suggest: [3]

- Blood transfusion should be conducted in children and adults with SCA prior to any surgical procedure involving anesthesia to bring the hemoglobin level to 10 g/dL.
- Among patients with HbSS disease undergoing surgery and who already have a hemoglobin level ≥ 8.5 g/dL without transfusion, are on chronic HU therapy, or are undergoing high-risk surgery such as neurosurgery, prolonged anesthesia, or cardiac bypass, a sickle cell expert should be consulted to determine the appropriate transfusion method.
- Among adults and children with HbSC or HbS/β^+-thalassemia, a sickle cell expert should be consulted to determine if full or partial exchange transfusion is required before a surgery involving general anesthesia.

b) Use in acute complications- Blood transfusion is used episodically in the cases of acute occurrences including stroke, multisystem organ failure, and ACS. NHLBI guidelines on acute blood transfusion therapy suggest:[3]

- Simple transfusion should be used in patients with symptomatic ACS combined with decreased hemoglobin of 1 g/dL below baseline, acute splenic sequestration plus severe anemia, or aplastic crisis.
- Exchange transfusion should be used in patients with symptomatic severe ACS.
- Simple or exchange transfusion can be adopted in cases of stroke, hepatic sequestration, intrahepatic cholestasis, and multisystem organ failure.
- Transfusion is not recommended in cases of uncomplicated painful crisis, priapism, asymptomatic anemia, and acute kidney injury (unless there is multisystem organ failure).

c) *Use in chronic complications*- Blood transfusion is used in chronic cases primarily involving primary and secondary prevention of stroke in children. NHLBI guidelines on chronic blood transfusion therapy suggest:[3]

- Simple or exchange transfusion should be used in children with Transcranial Doppler (TCD- time averaged mean maximal cerebral blood flow velocity) reading >200 cm/sec, and adults and children who had a previous clinically overt stroke.
- Chronic blood transfusion is not recommended in patients with recurrent splenic sequestration.

2.7.2.5 Health maintenance for patients with SCD

Health maintenance is especially important in patients with SCD as they are at a high risk for developing multisystem acute and chronic conditions associated with significant morbidity and mortality. Undetected signs and symptoms of diseases begin early in childhood among infants and children with SCD. The NHLBI expert panel report recommends screening for risk factors and early signs of complications so that measures can be taken to ameliorate complications and reduce

associated morbidity and mortality. According to the expert panel, screening should be conducted only for complications that are highly prevalent, clinically significant, and where sufficient evidence exists that early interventions in populations identified by screening are beneficial and effective. They also recommend that the screening methods used for detection of complications should be accurate, cost-effective, and cause minimal harm to the patient.[51]

Evidence from randomized controlled trials (RCTs) suggests that young children with SCA less than 5 years are at a high risk of contracting bacterial infections, meningitis, and septicemia. While the infections are not life threatening among SCA children with genotypes HbSC and HbS/β^0-thalassemia, they can be fatal in children with other genotypes. A meta-analysis reviewed findings from three RCTs and one observational study including a total of 951 children aged less than 5 years (HbSS-94%, HbSC-5% and HbS/β^0-thalassemia-1%). The study found that prophylactic antibiotic therapy significantly reduced the risk of pneumococcal infections in children with HbSS disease. [52, 53, 54]

Based on this evidence, NHLBI recommended the following guidelines regarding prophylaxis among SCA patients:[3]

a) Oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) should be administered twice daily in all children with SCD genotype HbSS until the age of 5. Prophylactic penicillin should be further continued in children with HbSS who have invasive pneumococcal infection.

b) Patients with SCD, their families, and caregivers are recommended to seek immediate medical care in cases of severe bacterial infections leading to fever.

c) Patients with SCD of all ages should be vaccinated against *Streptococcus pneumoniae.*

d) Patients with SCD should receive immunizations based on the harmonized immunization schedule by the Advisory Committee on Immunization Practices (ACIP).

Furthermore, NHLBI guidelines recommend that women and couples consider a "reproductive life plan" which entails their goals for having or not having children. As women with SCD face an increased risk of maternal morbidity and mortality and a higher risk of adverse pregnancy outcomes, they are encouraged to give more emphasis to a "reproductive life plan". They are also recommended to seek counseling for contraception to prevent unintended pregnancy and counseling about pregnancy associated risk of SCD complications.[3]

Additionally, the NHLBI expert panel identified relevant recommendations applicable to individuals with SCD from the United States Preventive Services Task Force (USPSTF) which focused on prevention and early recognition of chronic diseases. The recommendations are categorized based on specific age groups. Recommendations relevant to the patient population within this study have been included and are as follows:[55]

A. **USPSTF recommendations specific to children aged 3 to 12 years**

   a) Routine evaluation for amblyopia (decreased eyesight), strabismus (misalignment of the eyes), and defects in visual acuity should be conducted in children aged 3 to 5 years.

   b) Obesity screening should be conducted in children aged 6 years and older. Intensive counseling and behavioral interventions should be offered to affected children.

B. **USPSTF recommendations specific to adolescents aged 12 to 18 years**

   a) All sexually active adolescents should be screened for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections.

b) Sexually active girls/women should be screened for chlamydial and gonorrheal infections.

c) Depression screening should be conducted.

d) High-intensity behavior counseling, education, and interventions should be provided to prevent sexually transmitted infections, tobacco use, and obesity.

C. **USPSTF recommendations specific to adults aged 18 years and above**

a) Adults with SCD should be screened and provided behavioral counseling and interventions to reduce tobacco use, alcohol misuse, and obesity (BMI≥30 kg/m^2).

b) Adults at high risk for hepatitis C, hepatitis B, and/or HIV infections should be screened for these diseases.

c) Women at increased risk should be screened for breast cancer, cervical cancer, osteoporosis, and gonorrheal and chlamydial infections.

d) Adults should also be screened for colon cancer, cardiovascular diseases (hypertension), diabetes, and depression.[55]

2.7.3 National Institute of Health and Care Excellence Clinical Guideline

In June 2012, the National Institute of Health and Care Excellence (NICE) published a guideline for healthcare professionals and other staff providing care for people with SCD-related acute painful episodes in hospitals. In addition to clinical and patient-reported pain outcomes, NICE also considered health-related quality of life and cost-effectiveness while developing its guideline.[56]

The recommendations within this guideline are similar to the NHLBI guidelines with the exception of the following recommendations.[56]

i. The NHLBI guideline recommends the use of NSAIDS or non-opioid analgesics (in absence of contraindication) for moderate pain, while the NICE guideline recommends using weak opioids for patients with moderate pain who have not yet had any analgesia and strong opioid for those who have already had some analgesia before presentation.

ii. The NICE guideline suggests offering analgesia within 30 minutes to all patients presenting at the hospital with an acute painful sickle cell episode. The NHLBI suggests that patients should be offered analgesia within 30 minutes of triage and 60 minutes of registration.

iii. The NICE guideline recommends offering laxatives on a regular basis and anti-emetics as needed to address opioid side effects.

iv. The NICE guideline suggests using corticosteroids in the management of an uncomplicated acute painful sickle cell episode.

2.8 Types of Medications

The most frequently used medications for the management of SCD include HU and analgesics, both opioids and non-opioids. This section discusses each of these pharmacotherapies in detail, describing their classification (if any), mechanism of action, side effects, and current level of usage in SCD management.

2.8.1 Hydroxyurea

Hydroxyurea (Hydrea®, Droxia®) is a prominent drug therapy used in SCD management to reduce the frequency and severity of SCD-related complications, mainly VOC pain and ACS. HU is safe for use in infants, children, adolescents, and adults to reduce SCD-related symptoms. Initially approved as an antineoplastic agent, HU was approved by the US FDA for the indication

of SCD in 1998. Effectiveness of HU in SCD management has been since shown in at least three clinical trials and several other observational studies.[57]

Mechanism of Action

HU increases the level of fetal hemoglobin in patients with SCD, hence ameliorating SCD complications such as VOC pain and ACS. Before explaining the mechanism of action of HU, it is important to understand the role of fetal hemoglobin (HbF) in patients with SCD. SCD acute and chronic pain complications are the result of microvasculature obstruction by rigid sickled red blood cells. This phenomenon also leads to pulmonary embolism, further causing ACS. Among various genetic and environmental factors that affect the occurrence of VOC and ACS in patients with SCD, the level of HbF is one of the most prominent and beneficial. Studies conducted among Arab and Indian sickle cell patient populations have revealed that these patients have higher levels of HbF, and hence suffer from milder clinical manifestations of SCD as compared to American or Jamaican black patient populations.[58, 59]

To generate compelling evidence to support the role of HbF in SCD, Powars et al. published a study in 1984 that explored how the level of HbF in sickle cell patients impacted their SCD-related clinical manifestations.[60] The researchers followed 272 sickle cell anemia patients (age range: birth to 56 years) for 11 years providing clinical data for a total of 3,011 patient-years. The analysis revealed that the incidence rates of sickle cell crisis, ACS, and hospitalizations were consistently lower in patients with HbF value of ≥20 percent. Study findings suggested that parameters such as elevation of HbF can decrease the severity, improve the clinical course and general well-being of sickle cell anemia patients. The 1991 study by Platt et al. published in the *New England Journal of Medicine* also found that low HbF levels in patients were associated with

higher rates of pain episodes. It also suggested that these findings provide support for the use of HU and other treatments that increase the HbF level.[8]

Once the favorable effects of HbF levels in preventing SCD-related clinical complications (e.g., VOC pain, ACS) were established, subsequent research focused on identifying medications that increased HbF levels in patients with SCD. HU is one such drug that works by increasing the synthesis of HbF in blood, which in turn, inhibits the polymerization of sickle cell hemoglobin.[61] The first few clinical trials for HU use in SCD were conducted in the 1980s and early 1990s. The studies showed that blood levels of HbF increased in patients using HU, and the drug did not cause any short-term toxicity.[62] Several observational studies indicated additional benefits of HU such as lowering of number of circulating leukocytes and reticulocytes in the blood, altering the expression of adhesion molecules, raising red blood corpuscular volume, improving cellular deformability and rheology, and releasing nitric oxide. All of these actions lead to increased blood flow and local vasodilation, and reduced vaso-occlusion.[13, 63]

In 1995, a randomized, double-blind, placebo-controlled clinical trial called the Multicenter Study of Hydroxyurea (MSH) was published that later led to the approval of HU in SCD management. It was conducted among 299 adult patients with SCD, 152 and 147 patients in the treatment and control groups, respectively, who suffered three or more VOCs in a year. Table 2.3 below summarizes the findings of the trial. [13]

Table 2.3 Findings of Multicenter Study of Hydroxyurea (MSH) in Patients with SCD

Outcomes	**Hydroxyurea (N= 152)**	**Placebo (N= 147)**
Annual rate of pain crises	2.5 crises per year	4.5 crises per year
Time to crises • **Time to first crisis** • **Time to second crisis**	 3.0 months 8.8 months	 1.5 months 4.6 months
Incidence of ACS	25 (16.4%) patients	51 (34.7%) patients
Need for blood transfusion	48 (31.6%) patients	73 (49.7%) patients
Level of HbF	Increased from 5.0% to 8.6 %	Decreased from 5.2% to 4.7%
Hospitalization costs for pain	$12,160	$17,290

ACS- Acute chest syndrome, HbF-Fetal hemoglobin

[13] Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR, Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. New England Journal of Medicine. 1995 May 18;332(20):1317-22.

Furthermore, long-term follow-up studies on MSH participants, numerous observational studies, and another long-term clinical trial reported reduced mortality and increased survival among patients who used HU as compared to patients who did not.[64, 65, 66]

Hydroxyurea Therapy Side Effects and Adherence

Similar to most drugs, HU has side effects that affect patients' adherence to the therapy, and hence, negatively impacts outcomes. The NHLBI report combined evidence on HU toxicity from several sources, including three RCTs enrolling 517 patients with SCD, 47 observational studies enrolling over 3,000 patients with SCD, 21 RCTs enrolling more than 4,800 individuals without SCD, and 35 observational studies enrolling about 7,500 individuals without SCD. Table 2.4 summarizes the analysis of findings from the above-mentioned studies.[3]

Table 2.4 Evidence of Side Effects of Hydroxyurea in Sickle Cell Anemia

Potential Toxicity	Quality of the Evidence	Treatment Effect
Bone marrow suppression	High	Reversible cytopenias associated with hydroxyurea
Leukemia	No supporting evidence in SCD populations/Very low	The available evidence does not support the association of hydroxyurea treatment with the development of leukemia in adults or children
Leg ulcers	Adults: Moderate Children: Low	The available evidence does not support the association of hydroxyurea treatment with leg ulcers
Other side effects	Very low	Numerous other side effects were reported in the literature with low frequency and none with certain causality
Reproductive effects	Very low	Minimal human data exist on potential harmful reproductive effects of hydroxyurea in males and females

SCD- Sickle cell disease

[3] Adopted from National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014.

Even though HU is readily available and affordable, its use has been limited due to potential adverse effects and issues with patient adherence. A survey was conducted among 184 community-based and 30 university-based/affiliated hematologists/oncologists (H/Os) in Florida and North Carolina to determine practice patterns of HU use among adult patients with SCD. The study found that more than half (55%) of community H/Os prescribed HU in at least 10 percent of their patients. While HU was frequently prescribed for VOCs, chronic pain with narcotic use, and ACS, it was underutilized for indications such as stroke and pulmonary hypertension. The study identified several barriers to wider use of HU including physician concerns about carcinogenic potential, uncertainty about HU effectiveness, perceived patient apprehension about adverse effects, concern about lack of contraceptive use, and patient adherence. A more recent study published in 2012 suggested that only half the patients who were hospitalized for pain were taking HU, further indicating underutilization of HU. [12, 67]

In three drug effectiveness trials conducted among infants and children aged 18 years and below, HU adherence rates ranging between 74 and 94 percent were reported.[69,70,71] Another study, specifically assessing HU adherence and its effect on HbF levels among children 18 years and below, reported an adherence rate of 49 percent (based on pharmacy refills) and adherence rates were ≥ 75 percent using other methods such as a visual analog scale, the Morisky scale, medical provider report and clinic visits.[72, 73]

While drug effectiveness studies conducted in more controlled environments report high HU utilization and adherence rates, several retrospective observational database studies conducted among SCD children and adult populations within different states in the US reveal the contrary. [68, 74- 78] Candrilli et al. studied HU adherence and associated outcomes among patients with SCD enrolled in the North Carolina Medicaid program. Researchers found that mean MPR of HU was 60 percent and only 35 percent of the total 312 patients that participated in the study were HU adherent (i.e., MPR ≥0.80). Moreover, adherence to HU was significantly associated with reduced risk of VOC, SCD-related hospitalization, all-cause and SCD-related ED visits ($p<0.05$). Adherence to HU was also linked to reduced all-cause, SCD-related inpatient, ancillary care, VOC-related and total healthcare costs ($p<0.01$).[68] Another study conducted by Ritho et al. [74] among patients with SCD enrolled in the Florida Medicaid program examined HU adoption and utilization in patients aged 16-64 years. Low prevalence and persistence of HU use was reported with only 17 percent of the study cohort with at least one pharmacy claim for HU. The study also identified that 33 percent of patients (769/2301) from the study cohort were eligible to receive HU (i.e., had three or more hospitalizations for SCD) and further reported that out of these eligible patients with SCD, only 38 percent (292/769) received at least one HU prescription, only 31

percent (241/769) received at least two subsequent HU prescriptions and finally 15.4 percent had an MPR of ≥ 80 percent.[74]

Similarly, studies conducted using data from New York state Medicaid,[75] South Carolina Medicaid[76] and Missouri Medicaid[77] reported HU MPR of 67.8 percent (range: 9.3-100.0), 40 percent (range: 0.05-0.75) and 60.5 percent among children and adolescents with SCD, respectively. Furthermore, these studies revealed low HU utilization with only 40 percent, 15 percent and 8 percent of the study cohort being prescribed HU in the New York state Medicaid,[75] Maryland Medicaid[78] and South Carolina Medicaid studies,[76] respectively. Tripathi et al. found that only children with severe SCD complications were being prescribed HU as observed from South Carolina Medicaid data.[76]

In summary, HU is the most readily available, affordable and effective drug that can be used in SCD management. Adherence to HU has been associated with reduced healthcare utilization and costs. However, adherence using retrospective claims data has been suboptimal. NHLBI guidelines also recommend HU therapy among patients with SCD, especially in children up to the age of 12. Therefore, it is important to explore the temporal use of HU among patients of different age groups to identify if gaps in care exist.

2.8.2 Analgesics

Management of pain is a crucial and challenging aspect in SCD. Patients with SCD frequently suffer from conditions such as VOC and leg ulcers that could result in mild, moderate, or severe pain. Moreover, pain is associated with 90 percent of all hospital admissions among patients with SCD.[3] SCD-related pain is stabilized using pharmacological as well as non-pharmacological approaches. Non-pharmacological approaches to reduce pain include application

of heat or ice packs, relaxation, massage using menthol cream, vibration, therapeutic exercises, acupuncture, acupressure, distraction, listening to music, self-hypnosis, and transcutaneous electrical nerve stimulation (TENS). These methods help alleviate mild pain and are sometimes adopted along with pharmacological agents to reduce the amount of analgesic consumption for severe pain.[14,15]

Pharmacological agents used to manage SCD-related pain can be divided into two major categories: *opioid analgesics and non-opioid analgesics.*

2.8.2.1 Opioids

Opioid analgesics are used in the management of moderate to severe pain. These are among the most commonly used pharmacological agents in the management of acute and chronic pain among sickle cell patients. Opioids can be administered orally, intravenously, subcutaneously, and in some cases intramuscularly. While weak opioids are used in the treatment of moderate pain, strong opioids are used in the treatment of severe pain. These drugs are also used in patients with SCD with compromised renal function or who are at risk of acute renal failure as NSAIDs cannot be used in these patients. Codeine, a weak opioid, is the first line oral therapy used for home pain management in combination with other analgesics. Other opioid analgesics used to treat SCD-related pain include hydrocodone/acetaminophen combinations, hydrocodone/ibuprofen combinations, oxycodone, morphine, hydromorphone, oxymorphone, methadone, diamorphine, and fentanyl. Sustained-release oral opioids along with rescue analgesics are used in children as an effective alternative to parenteral opioids. The type of opioid, its dose, and route of administration should be assessed in individual patients based on past medical history and experience and severity of the pain. Table 2.5 below shows commonly used weak and strong opioid analgesics along with their usual dosage in adults. [14, 15]

Table 2.5 Opioid Analgesics for Mild, Moderate, and Severe Pain in Sickle Cell Disease

Opioid analgesic	**Usual starting dosage in adults**
Weak opioids for treatment of mild to moderate pain	
Codeine	30 to 60 mg every 3 or 4 hours; available in liquid or tablet form, alone or in combination with acetaminophen
Oxycodone	10 to 30 mg every 4 hours; Often used in combination with acetaminophen
Strong opioids for treatment of severe pain	
Morphine	*Oral dosage*- 15 to 30 mg every 4 hours *Parenteral dosage*- 0.1 to 0.15 mg per kg every 3 or 4 hours
Hydromorphone	*Oral dosage*- 2 to 4 mg every 4 to 6 hours *Parenteral dosage*- 1 to 2 mg every 4 to 6 hours
Meperidine	*Oral dosage*- 50 to 150 mg every 3 or 4 hours *Parenteral dosage*- 75 to 100 mg every 3 or 4 hours
Levorphanol	*Oral dosage*- 2 to 4 mg every 6 to 8 hours *Parenteral dosage*- Up to 1 mg intravenously every 3 to 6 hours; 1 to 2 mg intramuscularly or subcutaneously every 6 to 8 hours

[14] Adopted from Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. American Family Physician. 2000 Mar;61(5):1349-56.

Opioids exert their analgesic effects by acting on the central and peripheral nervous systems. Different opioid drugs bind with the mu, delta, or kappa opioid receptors located on the neuronal cell membranes in the brain, spinal cord, and other nervous tissue and inhibit the release of neurotransmitters. These neurotransmitters are responsible for the expression of pain and

sensitivity associated with mild, moderate, and severe pain. Hence, blocking the release of these neurotransmitters produces analgesic effect. However, opioid analgesics are accompanied with several side effects that lead to healthcare providers refraining from and/or restricting their use. These side effects include excessive sedation, nausea and vomiting, respiratory depression, bronchospasm, bradycardia, miosis, euphoria, constipation due to depression of gastrointestinal motility, pruritus and urinary retention. Some opioid analgesics also lead to dysphoria, hypertonia, tachycardia, tachypnea, and mydriasis. [16, 79]

The most controversial adverse effects associated with opioid analgesics are tolerance, addiction, and potential for abuse.[17] Opioid abuse could further lead to drug overdose and death. In 2008, the Centers for Disease Control and Prevention (CDC) reported that opioid analgesic use was involved in 73.8 percent of the total 20,044 prescription drug overdose deaths in the United States.[80] As opioid use is highly prevalent among patients with SCD, providers are concerned regarding the abuse of these drugs in this patient population. Often, they overestimate opioid dependence in these patients and fail to prescribe opioids appropriately. Opioids can be prescribed in combination with NSAIDs, in an effort to limit opioid consumption. This can result in undertreated SCD-related pain in many patients.[14, 81]

Ruta et al. utilized the CDC database to evaluate the use of opioids among patients with SCD and to determine the number of deaths among patients with SCD due to drug overdose from 1999 until 2013. They noted that while there were more than 14,700 deaths from opioid overdose among general patient population, only five patients with SCD died due to the same reason in 2008. While the number of deaths due to drug overdose increased among the general population, the trend was not observed in the SCD patient population during the years under study. They also noted that from the year 1999 until 2013, the highest number of deaths due to drug overdose in

patients with SCD was only 10 patients in a single year in 2010, 2011, and 2013.[82] Considering the US opioid epidemic, that has resulted in a significant increase in opioid-related overdoses and deaths, Akinboro et al. conducted a study to determine if opioid epidemic has impacted the rate of opioid-related inpatient mortality among patients with SCD. Interestingly, they found no increase in opioid-related inpatient death rates among patients with SCD over a 15-year period despite an increase in hospitalization rates for most adults with SCD over the same period. They also found that, unlike in the general population, where inpatient mortality rate from opioid-related hospitalizations increased over time, opioid-related inpatient deaths among patients with SCD were almost non-existent over the study period.[83]

To understand the current use of analgesics in SCD, a randomized, double-blind placebo-controlled multicenter study of HU in sickle cell anemia explored and recorded the at-home, acute care, and in-hospital analgesic use among 299 patients (aged 18-59 years) over a period of 790 days (2.16 years). Based on patients' diary records, the mean and median percent of days with analgesic use were 39.9 percent and 35.0 percent, respectively. Specifically, oral opioid use was reported in 10,071 (59.9%) of the total 16,818 biweekly follow-up visits. Oxycodone and codeine were the most commonly used opioids, reported in 23.2 percent and 18.3 percent of all biweekly follow-up visits, respectively; and together accounted for 61.7 percent of all analgesics used. Furthermore, during the 2,249 acute care/outpatient visits, treatment with parenteral opioids and oral opioids was used in 95.5 percent and 10.9 percent cases, respectively. The total percentage was more than 100 percent because multiple analgesics were used in some patients. Meperidine was the most commonly used parenteral opioid as it was used in 69.3 percent of acute care visits. Finally, during inpatient painful crises, parenteral opioids and oral opioids were used in 96.4

percent and 47.7 percent of cases, respectively. Table 2.6 summarizes the frequency of at-home opioid use reported in the study.[50]

Table 2.6 Frequency of At-Home Opioid Use

Opioid	**Frequency of use**	
	% of all diaries (n=16,818)	**% of diaries with any opioid use (n=10,071)**
Any opioid	59.9	100.0
Oxycodone	23.2	39.1
Codeine	18.3	31.0
Meperidine	6.7	11.4
Hydromorphone	6.6	11.2
Hydrocodone	5.4	9.0
Morphine	3.3	5.6
Methadone	1.4	2.3
Propoxyphene	0.9	1.6

[50] Adopted from Ballas SK, Bauserman RL, McCarthy WF, Castro OL, Smith WR, Waclawiw MA. Hydroxyurea and acute painful crises in sickle cell anemia: effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home. Journal of Pain and Symptom Management. 2010 Dec 1;40(6):870-82.

Another study by Smith et al. published in 2015 studied home opioid use self-reported in daily pain diaries among 219 adults with SCD enrolled between 2002 and 2004. They found opioid use in 78 percent (12,311 out of 15,778) of home pain days. In the study cohort, about 39 percent of patients used long-acting opioids with or without short-acting opioids, 47 percent used only short-acting opioids, about 10 percent used only non-opioid analgesics and about 5 percent used

no analgesics. Study findings also suggested significantly higher pain intensity and pain frequency and more frequent HU use among opioid users. [84] A more recent study by Ballas et al. found that the proportion of individuals with SCD with any opioid use was larger in age group 18-30 years as compared to age group less than 18 years, and then remained constant after age 30.[85] These findings further validate the extensive use of opioids to manage SCD-related pain among adults with SCD.

2.8.2.2 Non-opioids

Non-opioid analgesics are used in the management of mild pain. These agents mainly belong to a family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). They are widely available and used as analgesic, antipyretic and anti-inflammatory agents for a variety of disease conditions. Non-opioid analgesics used in the management of mild to moderate pain include agents such as acetaminophen, non-selective COX inhibitors (acetylsalicylic acid, ibuprofen, naproxen, and ketorolac), and selective COX-2 inhibitors such as celecoxib. These are also given in combination with opioid analgesics for severe pain. Table 2.7 below shows commonly used non-opioid analgesics along with their usual dosage in adults.[14, 15]

Table 2.7 Non-opioid Analgesics for Mild Pain in Sickle Cell Disease

Non-opioid analgesic	Usual dosage in adults
Acetaminophen	500 to 1,000 mg every 4 to 6 hours (maximum < 4,000 mg per day)
Acetylsalicylic acid (aspirin)	650 to 1,000 mg every 4 to 6 hours (maximum < 4,000 mg per day)
Diflunisal	1,000 mg initially, then 500 mg every 8 to 12 hours
Choline magnesium trisalicylate	1,000 to 1,500 mg every 12 hours
Ibuprofen	200 to 400 mg every 4 to 6 hours
Naproxen	500 mg initially, then 250 mg every 6 to 8 hours
Fenoprofen	200 mg every 4 to 6 hours
Ketoprofen	25 to 75 mg, then 250 mg every 6 to 8 hours (maximum < 300 mg per day)

[14] Adopted from Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. American Family Physician. 2000 Mar;61(5):1349-56.

NSAIDs exert analgesic effects through various peripheral and central mechanisms to inhibit the enzymes that are involved in prostaglandin synthesis. Prostaglandins are biological mediators responsible for inflammation and pain. NSAIDs such as ibuprofen, naproxen, and celecoxib inhibit prostaglandin synthesis by inhibiting the cyclooxygenase enzymes, COX-1 and COX-2, involved in prostaglandin synthesis.[86] There are about 20 commonly used NSAIDs which include long-acting or short-acting agents used for treatment of acute and chronic pain and inflammation associated with a number of disease conditions. While high-dose NSAIDs require a prescription, many low-dose forms are available over-the-counter for short term pain relief; and hence are easily accessible.

Although NSAIDs are effective in treating mild to moderate pain, they are accompanied by common side effects such as diarrhea, nausea, headache, dizziness, elevated liver enzymes, salt and fluid retention, and high blood pressure. Excessive and frequent use of NSAIDs can lead to severe harmful effects such as gastrointestinal ulcers, bronchospasm, rectal irritation, heart failure, hyperkalemia, reduced kidney function, confusion, and skin rash, reddening and itching.[87]

The multicenter study of HU was conducted among 299 adults with sickle cell anemia and three or more VOCs per year to study the effect of HU on frequency and severity of VOCs. The study reported treatment with NSAIDs in 9.2 percent of the total 2,249 outpatient acute care contacts (i.e., outpatient visits not leading to hospitalization). Moreover, NSAIDs were used in 11.3 percent of the total 2,209 painful crises. The study also compared NSAIDs utilization among treatment (patients prescribed HU) and control groups (patients given placebo). The treatment group was further divided into HU responders (patients with HbF level ≥15% at 18 months after initiation of treatment) and non-responders (patients with HbF level <15% at 18 months after initiation of treatment). Researchers showed that during outpatient acute care contacts, HU responders were more likely to use NSAIDs compared to HU non-responders (43.2% for responders versus 6.6% for non-responders, $p<0.0001$). Similar results were found in the placebo group (43.2% for responders versus 10.0% for non-responders, $p<0.0001$).[50]

2.9 Healthcare Utilization in Patients with SCD

Apart from its clinical implications, SCD is also associated with significant healthcare utilization and cost burden. Commonly used healthcare services among patients with SCD include emergency department visits, inpatient visits or hospitalization, outpatient visits and prescription drugs. A study by Kauf et al. estimated an average cost of $1,389 per patient-month among a population of children and adults with SCD, of which 51.8 percent of the care provided was SCD-

related.[5] Discussed below are some studies that provide estimates of healthcare utilization among patients with SCD.

Loeffler et al. conducted a study to determine the frequency of emergency department visits and hospital admission rates due to VOC. They noted a total of 727 visits among 154 patients with SCD during the study period (September 2013 through May 2015). They also identified that about three-fourths of these visits were by high users (n=44) which were defined as patients with four or more visits. The study findings reflected how patients with severe SCD may rely on emergency departments and hospital admissions to manage their complications.[88]

Interestingly, many previous studies have shown higher healthcare resource utilization, especially ED, inpatient and outpatient utilization, among young adults as compared to children and older adults. Brousseau et al. analyzed data on SCD-related ED and inpatient visits among a total of 21,112 patients obtained from the 2005-2006 Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases and State Emergency Department Databases. These databases included data from eight states, representing 33 percent of the US patients with SCD. The study revealed an average of 2.59 (95% confidence interval [CI]- 2.53-2.65) total encounters per patient per year, 1.52 (95% CI- 1.48-1.55) inpatient encounters, and 1.08 (95% CI- 1.04-1.11) ED visits. While 29 percent of the population had no encounters, 16.9 percent disproportionately accounted for three or more encounters per year. The study also found significantly higher utilization among publicly insured 18- to 30- year-olds who had 4.80 (95% CI- 4.58-5.02) encounters per patient per year. Table 2.8 summarizes the findings of this study.[89] As shown, encounters increased by age group with a peak at 18-30 years of age, followed by a decline in the older age groups.

Table 2.8 Rates of Acute Care Encounters by Age among Patients with Sickle Cell Disease

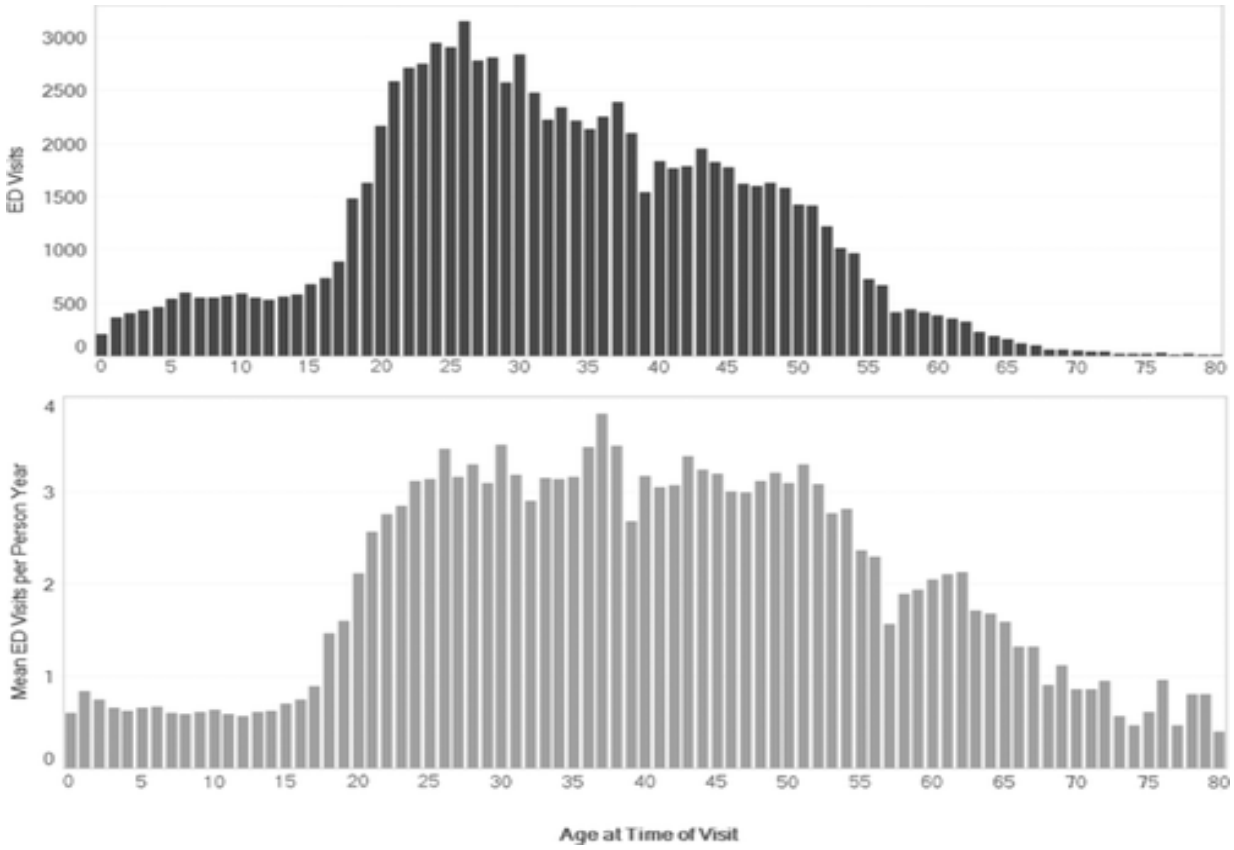
Age (in years)	ED visits per patient per year (95% CI)	Inpatient stays per patient per year (95% CI)	Total encounters per patient per year
1-9	0.59 (0.56-0.62)	0.91 (0.87-0.95)	1.50 (1.45-1.55)
10-17	0.68 (0.63-0.73)	1.37 (1.30-1.44)	2.04 (1.95-2.13)
18-30	1.59 (1.50-1.68)	2.02 (1.94-2.10)	3.61 (3.47-3.75)
31-45	1.29 (1.20-1.38)	1.65 (1.55-1.75)	2.95 (2.80-3.10)
46-64	0.86 (0.75-0.97)	1.23 (1.14-1.32)	2.09 (1.93- 2.25)

ED- Emergency Department; CI- Confidence Interval

[89] Adapted from Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. JAMA. 2010 Apr 7;303(13):1288-94.

Furthermore, a similar trend was observed in the study by Hemker et al., which found increased ED visits and lower outpatient visits among patients aged 18-19 years-old transitioning from pediatric to adult providers and young adults aged 20-30 years-old as compared to children aged <18 years-old and older adults aged 46 years and above.[90] Pope et al. concluded higher SCD-related morbidity and healthcare utilization during the transition from adolescence to young adulthood.[91] Lastly, a multisource longitudinal data study by Paulukonis et al. that examined pediatric and adult California patients with SCD found a threefold increase in mean annual ED visits in patients of age group 20- to 29.9-years-old as compared to patients of 10- to 19.9-years-old.[92] Figure 2.5 shows the emergency department utilization by Californians with SCD between 2005 and 2014.

Figure 2.5 Emergency Department Utilization by Californians with Sickle Cell Disease, 2005–2014



ED- Emergency Department

[92] Adopted from Paulukonis ST, Feuchtbaum LB, Coates TD, Neumayr LD, Treadwell MJ, Vichinsky EP, Hulihan MM. Emergency department utilization by Californians with sickle cell disease 2005–2014. Pediatric Blood & Cancer. 2017; 64:e26390..

Another study by Mvundura et al. evaluated healthcare utilization specifically among children with SCD and compared healthcare utilization and costs among children enrolled in Medicaid with those privately insured. Children were categorized into 1-5, 6-11- and 12-17-year age groups. The study found that the mean number of ED visits was 49 percent higher among children enrolled in Medicaid as compared to those with private insurance (1.36 vs. 0.91). The study also found that the mean number of outpatient visits between the two groups were similar (12.6 vs. 11.5) but mean expenditure on drug claims was significantly higher among Medicaid-insured children compared

to those who were privately insured ($1,049 vs. $ 531). Study findings are summarized in Table 2.9.[93]

Table 2.9 Annual Mean Utilization for Inpatient Care, Outpatient Care and Drug Claims for Children with Sickle Cell Disease, 2005

Type of insurance	ED visits per child	Inpatient admissions per child	Outpatient visits per child	Number of drug claims per child
Medicaid	1.36	0.91	12.6	21.0
Private Insurance	0.91	0.79	11.5	10.8

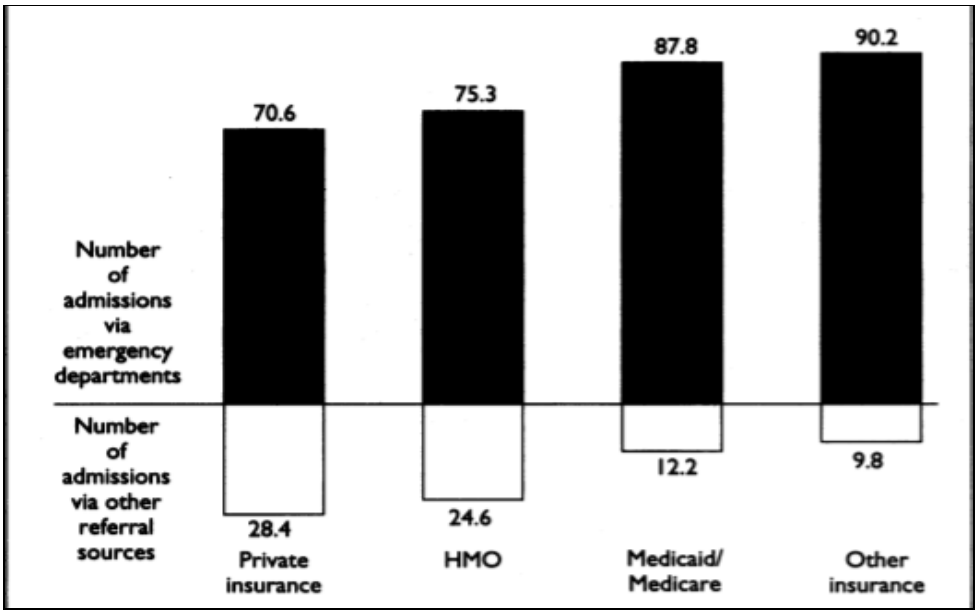
ED- Emergency Department

[93] Adapted from Mvundura M, Amendah D, Kavanagh PL, Sprinz PG, Grosse SD. Health care utilization and expenditures for privately and publicly insured children with sickle cell disease in the United States. Pediatric Blood & Cancer. 2009 Oct 1;53(4):642-6.

Furthermore, healthcare utilization among patients with SCD has been studied in individual states. Shankar et al. evaluated patterns of medical care utilization among children and adults with SCD in the state of Tennessee between from 1995 to 2002 and compared the rates of hospitalization and ED visits to those without SCD. The study reported that black patients with SCD had a 7-30 times higher rate of hospitalization and 2-6 times higher rate of ED visits ($p<0.001$) as compared to those without SCD. Hospitalization rates were about 1,000 per 1,000 population per year in children 5 years and younger, 600 per 1,000 in children aged 5-9 years, about 1,000 per 1,000 in adolescents aged 10-19 years, and 1,800 per 1,000 in adults aged 20-59 years. Patterns of ED visits were also similar, with the highest rates among the 10-19 and 40-59 years age groups.[94] Moreover, Woods et al. studied hospital utilization patterns among adult patients with SCD in Illinois for a study period of two years. The study found that ED visits were the primary source of hospital admission (85.7%) and the median number of hospital admissions

per patient was three. Figure 2.5 shows the insurance source of hospital admissions among patients with SCD in Illinois.[95]

Figure 2.6 Source of Admissions by Insurance Status, Hospitalized Sickle Cell Patients in Illinois, 1992-1993



HMO- Health maintenance organization

[95] Adopted from Woods K, Karrison T, Koshy M, Patel A, Friedmann P, Cassel C. Hospital utilization patterns and costs for adult sickle cell patients in Illinois. Public Health Reports. 1997 Jan;112(1):44.

Finally, Raphael at al. studied and compared healthcare utilization and costs between low-income children with SCD and other children of similar socioeconomic status without SCD using retrospective administrative claims data from a managed care plan serving low-income children covered by Medicaid and the State Children's Health Insurance Plan (SCHIP). The study reported that the percentage of children with SCD utilizing ED services was significantly higher than among children in the general population. While ED utilization among the general population ranged from 14 to 16 percent, ED utilization among the SCD population ranged from 37 to 43 percent ($p<0.0001$). Furthermore, 10 percent of children with SCD had at least one outpatient visit per year

with a hematologist for comprehensive specialty care. However, the study did not find a significant difference in the percentage of children receiving yearly well-child checks (preventive healthcare/wellness visit with pediatrician) between the two populations.[96]

2.10 Rationale for Study

Even though the life expectancy of patients with SCD has improved significantly in recent years, they still suffer from early mortality, substantial burden of complications,[2] and recurrent use of healthcare services. Findings from various studies in the literature reflected how patients with SCD complications rely on emergency departments, hospital admissions and outpatient visits, in addition to medications, to manage their complications. [88-90, 93-96]

Despite improvements in SCD care, the NHLBI report identified several gaps in the management of SCD and its complications.[3] Savage et al. summarized these gaps in care and noted areas that need further exploration. These include: overall opioid utilization (both alone and in combination with non-opioid and non-pharmacologic treatments), frequency of emergency department or hospital visits, effects on quality of life, preventive strategies for pain control, long-term opioid safety, and HU therapy's impact on analgesic use and overall healthcare utilization.[21]

Sickle cell disease requires both adequate pharmacological and non-pharmacological management. Preventing sickling of red blood cells to further avoid SCD complications, such as VOC, ACS and leg ulcers, currently remains an effective approach for the management of common SCD complications.[13, 57, 61, 63-66] Additionally, effective pain management plays a crucial role in reducing patients' suffering and improving their outcomes.[14, 15, 50] This study will describe temporal medication use patterns among patients with SCD of different age groups, in terms of index therapy and subsequent therapies.

Although previous studies have evaluated healthcare utilization among patients with SCD in other states, few have utilized a Texas SCD patient population. Raphael et al. studied healthcare utilization specifically among low income SCD children and adolescents with SCD in Texas, but the study did not include adult patients with SCD.[96] This study aims to determine differences in SCD-related healthcare utilization among children, adolescents and adult patient populations of Texas and assess how utilization differs by age groups. In addition, there is a lack of understanding on longitudinal temporal healthcare utilization among patients with SCD. This study aims to explore temporal healthcare utilization among patients with SCD in terms of ED visits, inpatient visits, outpatient visits and drug utilization. Studying the temporal healthcare utilization patterns can help determine if patients seek reactive care triggered by SCD complications or if they are proactive and adherent to therapies such as HU, which has been recommended by national SCD guidelines. Finally, findings from this study can be used to identify high utilizers of prescription drugs and overall SCD-related healthcare services.

2.11 Study Objectives and Hypotheses

The goal of this study is to describe temporal medication use patterns and other healthcare services use among Texas Medicaid recipients with SCD. The following are specific objectives and related hypotheses:

1. *Objective 1:* To describe SCD patient demographics (by SCD index drug type, i.e., HU, opioid analgesics, non-opioid analgesics) and medication and healthcare utilization.
2. *Objective 2:* To determine if there are differences in the type of SCD index therapy (HU, opioid analgesics, non-opioid analgesics, dual index therapy) by age group.

   H_{2A}: The proportion of patients using HU as index therapy decreases significantly with an increase in age groups.

H_{2B}: The proportion of patients using opioid analgesics as index therapy increases significantly with an increase in age groups.

Ho_{2C}: There is no significant difference in the proportion of patients using non-opioid analgesics as index therapy among the various age groups.

H_{2D}: The proportion of patients using dual drugs as index therapy increases significantly with an increase in age groups.

3. *Objective 3:* To determine if there are differences in SCD-related prescription drug utilization among patients by age group.

   H_{3A}: Adherence to HU decreases significantly with an increase in age group.

   H_{3B}: The mean total days' supply of opioid analgesics increases significantly with an increase in age groups.

   H_{3C}: The mean total days' supply of non-opioid analgesics increases significantly with an increase in age groups.

4. *Objective 4:* To determine whether there are differences in SCD-related healthcare utilization among patients by age group.

   H_{4A}: The proportion of patients with one or more SCD-related emergency department visits increases significantly with an increase in age groups.

   H_{4B}: The proportion of patients with one or more SCD-related hospital admissions increases significantly with an increase in age groups.

   H_{4C}: The number of SCD-related outpatient visits increases significantly with an increase in age groups.

   H_{4D}: The mean number of all-cause prescription medications increases with increase in age groups.

5. *Objective 5* (exploratory): To describe temporal use of healthcare services after an ED visit or hospitalization.

CHAPTER THREE: METHODS

3.1 Chapter Overview

This chapter covers the description of the methods used in the study including the study design, data source, population, index date, inclusion criteria, and data analysis. The chapter also provides operational definitions of the study variables, sample size calculations, statistical methods that will be employed to address the study objectives, and potential limitations of this study.

3.2 Institutional Review Board Approval

Approval for conducting this study was obtained from The University of Texas at Austin Institutional Review Board. The study has minimal risk to the welfare and privacy of the subjects since the retrospective claims data from Texas Medicaid database are de-identified.

3.3 Study Design and Data Source

This study was a retrospective secondary database analysis of medical and prescription claims using Texas Medicaid administrative claims database. The study participants were Texas Medicaid recipients with at least one inpatient or outpatient diagnosis for SCD. Medicaid is a health insurance program that has joint funding through federal and state governments. It provides medical coverage to low-income individuals, non-disabled children, caregivers of dependent children, low-income pregnant women and the elderly. For fiscal year 2017, approximately 4.1 million non-elderly individuals (i.e., 64 years of age and below) were covered by Texas Medicaid.[97, 98] In terms of age and ethnicity, the majority of enrollees were children (~76%) and Hispanic (51%) in fiscal year 2015.[99]

3.3.1 Inclusion Criteria

The study population is Texas Medicaid recipients. Patients were included if they:

1. were equal to or greater than 2 years and less than or equal to 63 years of age at the index date;
2. were continuously enrolled in Medicaid (with medical and pharmacy coverage) for at least six months pre-index and twelve months post-index;
3. had at least one inpatient SCD or one outpatient SCD diagnosis during the study period (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 280.60-282.69, 282.41, 282.42 or ICD-10 D57.xx);
4. had no SCD-related prescription or medical claims within the six months pre-index period.

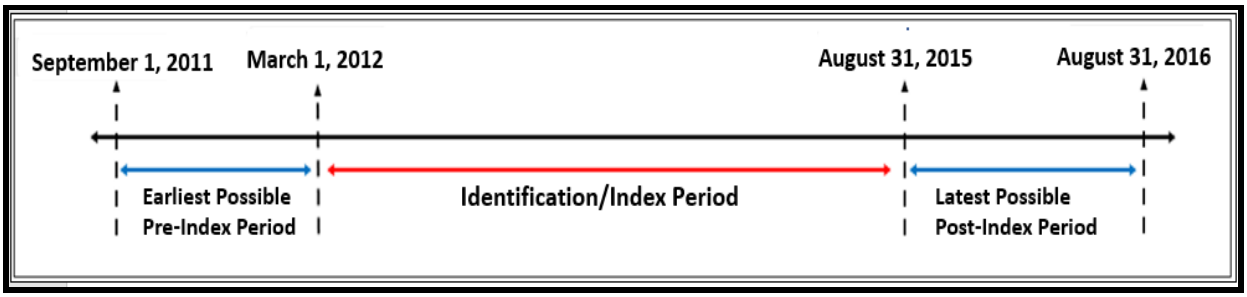
3.3.2 Index Date

For Objectives 1-4, the index date was defined as the date of dispensing of the first SCD-related drug (HU, opioid analgesic, non-opioid analgesic, or dual index therapy) within the identification period from 3/1/2012 – 8/31/2015 (Figure 3.1). A duration of six months before the index date was defined as the pre-index period when patients were not dispensed any SCD-related drug (HU, opioid analgesic, non-opioid analgesic). Patients were followed for 12 months after the index date in order to observe their medication use patterns and healthcare resource utilization. For Objective 5, patients with SCD-related ED or inpatient visits within the 12-month post-index follow-up period were identified. For these patients, the index service date was defined as the date of the first ED or inpatient visit with an SCD diagnosis after the index date within the follow-up period. These patients were followed for varied lengths of time until the end of the 12-month follow-up period. These patients would have SCD-related drugs in the pre-index period but will not have SCD-related inpatient or ED visit before the index service date. The index date and index service date were unique for each subject.

3.3.3 Data Collection

Data were retrieved from Texas Medicaid inpatient, outpatient, eligibility, and prescription data files. Based on the previously stated information, prescription and medical claims were utilized for the purposes of subject identification. Hence, these four files were merged using the unique recipient identification number that united all files. The following data from the enrollment file were included: year of birth, gender, and dates of eligibility. Data from Texas Medicaid was extracted from September 1, 2011 to August 31, 2016. Subjects were identified using data from the identification period (March 1, 2012 to August 31, 2015)**.** Prescription and medical claims for each subject were analyzed over an 18-month study period (i.e., the 6-month pre-index and 12-month post-index periods) (Figure 3.1).

Figure 3.1 Data Extraction and Subject Identification Period



Prescription claims for SCD-related medications were identified by the following data: the American Hospital Formulary Service (AHFS) code and Generic Code Sequencing Number (GCN_Seq No). Some of the most commonly used drugs in SCD management are listed in Table 3.1.

Table 3.1 SCD-related Medications Available through Medicaid Vendor Drug Program

SCD medication class	Generic Name	Brand Name
Hydroxyurea		
Hydroxyurea	Hydroxyurea	Droxia®, Hydrea®
Opioid Analgesics		
Opioid analgesics	Codeine and combinations-Acetaminophen-Codeine #2, Acetaminophen-Codeine #3, Acetaminophen-Codeine #4, Aspirin, Butalbital, Caffeine with Codeine	Capital with Codeine, Carisoprodol-Aspirin-Codeine, Fiorinal-Codeine, Tylenol with Codeine #3®, Tylenol with Codeine #4®
	Oxycodone and combinations-Oxycodone, Oxycodone-Acetaminophen, Oxycodone-Aspirin, Oxycodone-Ibuprofen	Endocet®, Oxycontin®, Percocet®, Roxicodone®, Xartemis XR®, Xtampza ER®
	Morphine	Embeda ER®, Kadian ER®, MS Contin®
	Hydrocodone and combinations-Hydrocodone-Acetaminophen, Hydrocodone-Ibuprofen	Hysingla®, Ibudone®, Lorcet®, Norco®, Reprexain®, Vicodin®, Xodol®
	Fentanyl-Fentanyl, Fentanyl citrate	Actiq®, Duragesic®, Fentora®, Lazanda®, Subsys®
	Meperidine	Demerol®
	Methadone	Dolophine®
Non-opioid Analgesics		
Acetaminophen	Acetaminophen-Butalbital-Acetaminophen, Butalbital-Acetaminophen-Caffeine	Acephen®, Aceta-gesic® Allzital®, Bupap®, Child Pain-Fever®, Children's MAPAP®, Children's Q-PAP®, ED-APAP®, Esgic®, Fioricet®, Infant Pain-Fever®, Junior MAPAP®, Tylenol®, Zebutal®
NSAIDs	Ibuprofen	Children's Ibuprofen®, Advil®, Motrin®
	Ketorolac	Toradol
	Naproxen	All Day Pain Relief®, Anaprox®, EC-Naprosyn®, Aleve®
	Aspirin	Aspirin®, Butalbital-Aspirin-Caffeine, Fiorinal®
	Celecoxib	Celebrex®

NSAIDs- Non-Steroidal Anti-Inflammatory Drugs

[100] Information obtained from Texas Health and Human Services, Vendor Drug Program.

3.4 Study Variables

Below is a description of the study's dependent and independent variables followed by operational definitions (see Table 3.2).

3.4.1 Dependent Variables

The dependent variables include: (1) SCD index drug type; (2) SCD-related prescription drug utilization; (3) SCD-related healthcare service utilization; and (4) all-cause prescription drug utilization.

SCD index drug type included HU, opioid analgesics, non-opioid analgesics, and dual index therapy (i.e., more than one SCD-related drug dispensed on the index date). These drugs were chosen based on the therapies recommended by the National Institutes of Health National Heart, Lung, and Blood Institute (NIH- NHLBI) evidence-based expert panel report.[3] SCD-related drug types include: HU (Droxia®- 200 mg, 300 mg, 400 mg; Hydrea®- 500 mg, generic HU), opioid analgesics (codeine, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxycodone, morphine, hydromorphone, oxymorphone, methadone, diamorphine, fentanyl, propoxyphene, meperidine), and non-opioid analgesics (acetaminophen, ibuprofen, ketorolac, acetyl salicylic acid, naproxen, celecoxib, butalbital and combinations). Also see Table 3.1.

SCD-related prescription drug utilization was assessed for each of the drug types. For HU, adherence was measured using the medication possession ratio (MPR) since this drug is recommended to be taken on a chronic basis. In general, the two most common approaches for assessing adherence in large databases are MPR and proportion of days covered (PDC). MPR can be defined as the sum of total days' supply for all fills divided by the number of days in the observation period (Figure 3.2). PDC is determined by dividing the number of days the drug was available by the number of days in the specific interval or study period.[101] While PDC is a more conservative method of adherence estimation compared to MPR for multiple medication use, drug switches, or therapeutic duplication, it typically provides the same adherence values as MPR for

monotherapy. As this study involved adherence assessment of HU only (i.e., monotherapy), MPR was used.

Figure 3.2 Formula for Calculating Medication Possession Ratio (MPR)

MPR = Sum of total days' supply for all fills x 100 / Number of days in study period

For opioid and non-opioid analgesics, which are used on an as needed basis, mean total days' supply was used to assess SCD-related prescription drug utilization. Mean total days' supply for SCD-related analgesics was calculated as the sum of total days' supply for all fills within the observation period (365 days). For fills toward the end of the observation period, days' supply was truncated if it went past the end of the observation period.

Furthermore, SCD-related healthcare service utilization was calculated as proportion of patients having one or more SCD-related ED visits, proportion of patients having one or more hospitalizations, and the mean number of SCD-related outpatient visits. Also, the mean number of all-cause unique prescription medications was calculated.

Finally, temporal SCD-related healthcare service utilization was evaluated as proportion of patients having an SCD-related ED visit or hospitalization as their index service during the follow-up period. Within the patient groups that received ED or hospitalization as index service, the proportions of patients having ED visits, hospitalizations, outpatient visits or prescription drugs as their subsequent healthcare services were also calculated.

3.4.2 Independent Variables

Age group (i.e., 2-12, 13-17, 18-24, 25-40, 41-63) served as the primary independent variable. Age group was used as a primary independent variable because guidelines for SCD medication use (HU and opioid analgesics) differ based on age groups of patients with SCD. In addition, previous studies have assessed healthcare utilization among patients with SCD of

different age groups. Hence, it seemed pertinent to explore real-world medication and healthcare utilization in SCD by age group. It also facilitated identifying gaps in care and where interventions may be needed. Gender (male/female) was assessed for descriptive purposes only.

Table 3.2 Operational Definitions of Study Variables

Variables	Operational Definition
Dependent Variables	
Index Drug type (Objectives 1-2) (Categorical)	1=Hydroxyurea; 2= Opioids; 3=Non-opioid analgesics; 4=Dual analgesic therapy See Table 3.1
SCD Prescription Drug Utilization (Objective 3)	
Adherence to Hydroxyurea (Continuous)	Medication adherence (calculated as MPR) to hydroxyurea in the post-index period *Numerator:* The sum of the days' supply for all hydroxyurea claims dispensed starting with the index date and concluding with the last fill within the 12-month post index period. *Denominator:* 365 days (12-month post index period). In the event that the calculated ratio is larger than 1.0, MPR will be truncated at 1.0.
Total days' supply of opioid analgesics (Continuous)	Mean total days' supply of opioid analgesics in the post-index period: The sum of the days' supply for all opioid analgesic claims from the index date to the last fill within the 12-month post index period.
Total days' supply of non-opioid analgesics (Continuous)	Mean total days' supply of non-opioid analgesics in the post-index period: The sum of days' supply for all non-opioid analgesic claims from the index date to the last fill within the 12-month post index period.
Healthcare Utilization (Objective 4)	
SCD-related ED visits (Continuous)	Number of emergency department visits with an SCD diagnosis code
SCD-related inpatient hospital admissions (Continuous)	Number of inpatient/hospital visits with an SCD diagnosis code
SCD-related outpatient visits (Continuous)	Number of outpatient visits with an SCD diagnosis code
All-cause prescription drug utilization (Continuous)	Number of all-cause unique prescription medications in the post-index period
Demographics and Independent Variable	
Age groups (Objectives 2-4)	Age at Index (Continuous) Age groups- 2-12; 13- 17; 18- 24; 25-40; 41-63 (Categorical)
Gender (Categorical)	1= Female, 0=Male

3.5 Statistical Analysis

Several statistical analyses were used to address the study objectives. Power analyses were also conducted (Table 3.3). All statistical tests were performed with SAS version 9.4 (SAS Institute, Cary, NC). Statistical tests were two-sided with an a priori significance level of $p<0.05$. Frequencies and histograms were used to check for data abnormalities and normality. A summary of objectives, hypotheses and statistical tests that were used is presented in Table 3.4 (located at the end of this chapter).

Descriptive statistics (mean, standard deviation and frequency) were used to address Objective 1 and Objective 5. Demographic characteristics, medication utilization and healthcare service utilization patterns (Objectives 2-3) provide a general overview of Texas Medicaid recipients with SCD. The study describes temporal medication (Objective 2) and healthcare utilization patterns (Objective 4) among patients with SCD of varying age groups for the study period. In addition, the results describe temporal use of healthcare services among patients with SCD after an ED visit or hospitalization (Objective 5).

3.5.1 Statistical Tests Assumptions and Sample Size Calculations

This section includes the test assumptions and sample size calculations for the statistical tests presented in Table 3.3. Objectives 1 and 5 did not involve sample size calculations because they are descriptive. Chi-square, one-way analysis of variance (ANOVA) and Kruskal-Wallis test (for non-parametric data) were used to address Objectives 2–4 and sample size calculations for these tests are discussed below.

3.5.1.1 Chi-Square Test

A chi-square test was employed for Objective 2 to determine if there were overall differences in the proportions of patients using different SCD-related drug types (HU vs. opioid analgesics vs. non-opioid analgesics vs. dual index therapy) among 5 different age groups (i.e., 2-12, 13-17, 18-24, 25-40, 41-63 years). The following assumptions for a chi-square test are required: 1) frequency or count data; 2) categorical variables; 3) independent and mutually exclusive study groups; and 4) adequate sample size, i.e., no more than 20 percent of cells having an expected frequency less than five and no single cell having an expected frequency less than one.[102] For the purpose of this study, a medium effect size (f = 0.30) was assumed to achieve sample size estimation according to Cohen's convention.[103] Using the G-Power software, given an alpha level of 0.05 and power of 0.8, with 8 degrees of freedom [df= (r-1)(c-1)= (3-1)(5-1)= 8)] the required total sample size was 167 (~12 subjects per cell).[104] If the chi-square test was significant, pairwise chi-square comparisons were performed to identify which groups differed significantly from each other. To restrict the family-wise error rate to 0.05, a smaller alpha level was used for individual pairwise chi-square comparisons that was calculated by dividing 0.05 by the number of comparisons (e.g., if α-level for 10 pairwise chi-square comparisons= 0.05/10= 0.005).

3.5.1.2 Analysis of Variance (ANOVA)

To address objectives 3 and 4, analysis of variance (ANOVA) was employed. The assumptions for ANOVA are: 1) independence of observations; 2) a normal distribution and constant variance of the errors; and 3) homoscedasticity or homogeneity of variance.[105] For the purpose of this study, a medium effect size (f = 0.25) was assumed to achieve sample size estimation according to Cohen's convention.[103] Using the G-Power software, given an alpha level

of 0.05, and power of 0.8, with 5 age groups (i.e., 2-12, 13-17, 18-24, 25-40, 41-63 years) the required total sample size was 200 (40 subjects per group).[104] Furthermore, if needed, Duncan's post-hoc analyses were performed to determine which groups were significantly different than others. Kruskal-Wallis test was used if data was distributed non-parametrically. The sample size required for Kruskal-Wallis test is determined by multiplying the sample size calculated for an equivalent parametric test, ANOVA, by a correction factor referred to as the asymptotic relative efficiency (ARE).[106] Hence, using ARE of 0.955 for ANOVA, sample size required for Kruskal Wallis test was 200*0.955= 191.

Table 3.3 Summary of Estimated Sample Sizes for the Statistical Tests

Statistical analytical tests	**Chi-square**	**ANOVA**	**Kruskal-Wallis**
Required sample size	167	200	191

Based on the sample size estimates calculated for different analyses, a sample size of at least 200 (for ANOVA) was required to detect a statistically significant difference if present.

Table 3.4 Summary of Objectives, Hypotheses, and Statistical Tests

Objective	Hypotheses	Dependent Variable	Independent Variable	Procedure/Statistical Test
1. To describe SCD patient demographics (by SCD index drug type, i.e., HU, opioid analgesics, non-opioid analgesics) and medication and healthcare utilization.	N/A	Drug type (hydroxyurea vs. opioid analgesics vs. non-opioid analgesics)	Age (continuous)	Descriptive statistics: Means, standard deviation
	N/A	Drug type (hydroxyurea vs. opioid analgesics vs. non-opioid analgesics)	Gender (nominal)	Frequencies
	N/A	Medication utilization (Adherence to hydroxyurea, total days' supply of opioid and non-opioid analgesics)	N/A	Descriptive statistics: Means, standard deviation, Median
	N/A	SCD-related healthcare service utilization (emergency department visits, hospitalizations, outpatient visits, all-cause prescription medications)	N/A	Descriptive statistics: Means, standard deviation, Median Frequencies
2. To determine if there are differences in the type of SCD index therapy (HU, opioid analgesics, non-opioid analgesics, dual index therapy) by age group.	**H_{2A}:** *The proportion of patients using hydroxyurea as index therapy decreases significantly with an increase in age groups.*	Proportion of index hydroxyurea prescriptions	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction
	H_{2B}: *The proportion of patients using opioid analgesics as index therapy increases significantly with an increase in age groups.*	Proportion of index opioid analgesic prescriptions	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction

Table 3.4, continued

Objective	Hypotheses	Dependent Variable	Independent Variable	Procedure/Statistical Test
	Ho_{2C}: *There is no significant difference in proportion of patients using non-opioid analgesics as index therapy among various age groups.*	Proportion of index non-opioid analgesic prescriptions	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction
	H_{2D}: *The proportion of patients using dual drugs as index therapy increases significantly with an increase in age groups.*	Proportion of dual index therapy (opioid + non-opioid prescriptions)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction
3. To determine if there are differences in SCD-related prescription drug utilization among patients by age group.	**H_{3A}:** *Adherence to hydroxyurea decreases significantly with an increase in age groups.*	Adherence to hydroxyurea (Medication Possession Ratio) (continuous)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	ANOVA/Kruskal-Wallis test (depending on if the data distribution is parametric or non-parametric); Duncan's post-hoc analysis for parametric data/ Pairwise chi-square comparisons with family-wise error rate of 0.05 for non-parametric data
	H_{3B}: *The mean total days' supply of opioid analgesics increases significantly with an increase in age groups.*	Mean total days' supply of opioid analgesics (continuous)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	ANOVA/Kruskal-Wallis test (depending on if the data distribution is parametric or non-parametric); Duncan's post-hoc analysis for parametric data/ Pairwise chi-square comparisons with family-wise error rate of 0.05 for non-parametric data

Table 3.4, continued

Objective	Hypotheses	Dependent Variable	Independent Variable	Procedure/Statistical Test
	H_{3C}: *The mean total days' supply of non-opioid analgesics increases significantly with an increase in age groups.*	Mean total days' supply of non-opioid analgesics (continuous)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	ANOVA/Kruskal-Wallis test (depending on if the data distribution is parametric or non-parametric); Duncan's post-hoc analysis for parametric data/ Pairwise chi-square comparisons with family-wise error rate of 0.05 for non-parametric data
4. To determine whether there are differences in SCD-related healthcare utilization (ED visits, inpatient visits, outpatient visits, all-cause prescription drug utilization) among patients by age group.	**H_{4A}:** *The proportion of patients with one or more SCD-related ED visits increases significantly with an increase in age groups.*	Proportion of patients with one or more ED visits with SCD diagnosis code	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction
	H_{4B}: *The proportion of patients with one or more SCD-related hospital admissions increases significantly with an increase in age groups.*	Proportion of patients with one or more inpatient visits with SCD diagnosis code	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	Chi-square test; Pairwise chi-square comparisons with reduced alpha level to maintain family-wise error rate of 0.05/Bonferroni correction
	H_{4C}: *The number of SCD-related outpatient visits increases significantly with increase in age groups*	Mean number of outpatient visits with SCD diagnosis code (continuous)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	ANOVA/Kruskal-Wallis test (depending on if the data distribution is parametric or non-parametric); Duncan's post-hoc analysis for parametric data/ Pairwise chi-square comparisons with family-wise error rate of 0.05 for non-parametric data

Table 3.4, continued

Objective	Hypotheses	Dependent Variable	Independent Variable	Procedure/Statistical Test
	H_{4D}: *The mean number of all-cause prescription medications increases with increase in age groups.*	Mean number of all cause prescription medications (continuous)	Age group (categorical 2-12 vs. 13-17 vs. 18-24 vs. 25-40 vs. 41-63)	ANOVA/Kruskal-Wallis test (depending on if the data distribution is parametric or non-parametric); Duncan's post-hoc analysis for parametric data/ Pairwise chi-square comparisons with family-wise error rate of 0.05 for non-parametric data
5. To describe temporal use of healthcare services after an ED visit or hospitalization.	N/A	Proportion of patients using healthcare services (ED visits or hospitalizations as index service) (ED visits, hospitalizations, outpatient visits, or prescription drug utilization as subsequent services)	N/A	Descriptive statistics: Frequencies

SCD=Sickle Cell Disease; **ED**=Emergency Department; **ANOVA**= Analysis of Variance

CHAPTER FOUR: RESULTS

4.1 Chapter Overview

This chapter presents the results of the study and describes SCD medication and healthcare services utilization patterns among Texas Medicaid recipients with SCD. First, patient inclusion criteria and attrition are presented. Second, patients' demographic and medication and health service utilization characteristics will follow. Finally, the study objectives and the results of all statistical analyses are presented.

4.2 Final Study Sample

The initial population was comprised of 11,995 Texas Medicaid recipients with a diagnosis of SCD or sickle cell trait (SCT) during the study period. Of these, 3,450 patients (28.8%) did not have any SCD-related prescription drugs (hydroxyurea, opioid and non-opioid analgesics) during the study period, resulting in a sample size of 8,545 subjects. Further, of the 8,545 patients, only 4,466 (52.3%) patients received their first SCD-related drug within the identification period. After applying the remaining inclusion criteria, the final study sample was comprised of 2,339 patients, which will be used to address Objectives 1-4 (Table 4.1). For Objective 5, 801 patients out of the study sample of 2,339 patients were identified who had SCD-related ED or inpatient visits during the 12-month post-index follow-up period (Table 4.1).

Table 4.1 Patient Attrition among Texas Medicaid Recipients

Inclusion Criteria	**Included Patients** N (% of total [a])	**Excluded Patients** N (% of total [a])
SCD or (Sickle Cell Trait) diagnosis between 9/1/11 to 8/31/16 with prescription drugs	11,995	
First SCD-related drug dispensed during the study period (9/1/11 to 8/31/16) [b]	8,545 (100.0)	3,450 (0.0)
First SCD-related drug dispensed during the identification period (3/1/12 to 8/31/15)	4,466 (52.3)	4,079 (47.7)
Age (at the index date: first SCD-related drug) between 2-63 years	3,242 (37.9)	1,224 (14.3)
Continuously enrolled for 6 months pre-index and 12 months post-index [c]	2,343 (27.4)	899 (10.5)
1 inpatient or 1 outpatient visits with SCD diagnosis (during the index period: /1/12 – 8/31/15)	2,343 (27.4)	0 (0.0)
Patients with gender coded as both male and female	2,339 (27.4)	4 (0.1)
FINAL SAMPLE (Objectives 1-4)		**2,339**
ED or hospitalization during the identification period (3/1/12 to 8/31/15) [d]	**801** (9.4)	1,538 (18.0)
FINAL SAMPLE (Objective 5)		**801**

SCD = Sickle Cell Disease, ED=Emergency Department
[a] Total N=8,545
[b] SCD-related drugs include hydroxyurea, opioid and non-opioid analgesics
[c] Index date for the primary objectives is the date of dispensing of first SCD-related drug within the identification period (3/1/12 – 8/31/15)
[d] Index date for the secondary objective is date of first SCD-related emergency department visit or hospitalization within the identification period (3/1/12 – 8/31/15); Follow-up period varies per patient and ends 8/31/16

4.3 Study Objectives

4.3.1 Objective 1: Demographic and Healthcare Utilization Characteristics

Objective 1 was to describe SCD patient demographic characteristics (age, gender), medication utilization (i.e., number of index drug users, adherence, and total days' supply), and healthcare service utilization (ED, inpatient and outpatient visits, and all-cause prescription medications). Characteristics of the final sample are shown in Table 4.2.

4.3.1.1 Demographic characteristics

Overall, mean age was 19.1 (± 14.6) years and the highest proportion of patients were in the 2-12 age group (41.3%). Almost two-thirds (62.5%) of the sample were female.

4.3.1.2 Medication and healthcare service utilization characteristics

With respect to index drug therapy type, the highest proportion of the patients were prescribed opioid analgesics 1,069 (45.7%), followed by non-opioid analgesics (36.6%). About 11 percent patients received dual index therapy, i.e., they were prescribed both opioid and non-opioid analgesics on their index date. Only 6.5% were prescribed HU.

Utilization of HU was measured in terms of the medication possession ratio (MPR) which was 47.5% (± 31.4) and only 20.7 percent had an MPR ≥ 80%. As there was large variation in the mean total annual days' supply of opioid (47.5 ± 103.6) and non-opioid (31.9 ± 53.8) analgesics, both mean and median were reported. The median number of opioid and non-opioid analgesic prescriptions were 10 and 15, respectively.

Regarding healthcare service utilization among the study sample, 703 (30.1%) patients had one or more SCD-related ED visits with mean number of 1.2 (± 4.5) visits in the 12-month post-index period and the median was 0. Moreover, 503 (21.5%) patients had one or more SCD-related inpatient visits with mean number of 1.8 (± 6.9) visits in the 12-month post-index period and the median was 0. The mean number of SCD-related outpatient visits within the 12-month post-index period was 4.0 (± 8.4), and mean number of all-cause prescription medications dispensed within the 12-month post-index period was 14.3 (± 12.0).

Table 4.2 Demographic, Medication and Healthcare Service Utilization Characteristics (All Patients with SCD N=2,339)

Patient Characteristics	**All Patients with SCD N=2,339**
Demographic Characteristics	
Age at index date	
Mean ± SD, year	19.1 ± 14.6
Age groups, N (%)	
2-12 years	965 (41.3)
13-17 years	272 (11.6)
18-25 years	375 (16.0)
26-40 years	483 (20.7)
41-63 years	244 (10.4)
Total	2,339 (100.0)
Gender, N (%)	
Female	1,461 (62.5)
Male	878 (37.5)
Total	2,339 (100.0)
Medication Utilization Characteristics	
Index drug type, N (%)	
HU users	153 (6.5)
Opioid users	1,069 (45.7)
Non-opioid users	855 (36.6)
Dual index therapy users	262 (11.2)
Total	2,339 (100.0)
SCD-related Prescription Drug Utilization	
HU MPR, Mean (SD)	47.5 (31.4)
HU MPR ≥ 80%, %	20.7
Mean annual total days' supply: Opioids, Mean (SD) Median	47.5 (103.6) 10.0

Table 4.2, continued

Patient Characteristics	**All Patients with SCD N=2,339**	
Mean annual total days' supply: Non-opioids, Mean (SD) Median	31.9 (53.8) 15.0	
SCD-related Healthcare Service Utilization	**N**	**%**
Emergency Department Visits (Mean ± SD) ***Median***	**1.2 ± 4.5** **0.0**	
Yes	703	**30.1**
No	1636	69.9
1	285	12.2
2	150	6.4
3	91	3.9
4	39	1.7
5	27	1.2
6+	111	4.7
Hospitalizations (Mean ± SD) ***Median***	**1.8 ± 6.9** **0.0**	
Yes	503	**21.5**
No	1836	78.5
1	103	4.4
2	79	3.4
3	63	2.7
4	51	2.2
5	30	1.3
6+	177	7.5
Outpatient visits (Mean ± SD) ***Median***	**4.0 ± 8.4** **1.0**	
All-cause prescription medications (Mean ± SD)	**14.3 ± 12.0**	

SCD=Sickle cell disease
HU=Hydroxyurea
MPR=Medication Possession Ratio

4.3.1.3 Demographic characteristics by index drug type

Objective 1 included a description of SCD patient demographics (age, age group, gender) by SCD index drug type as shown in Table 4.3. While index HU users were the youngest with a mean age of 14.1 (± 11.9) years, index opioid users were the oldest with a mean age of 22.3 (± 15.3) years. Across all index drug types, the proportion of females was equal to or higher than that of males, ranging from about 50% in the HU group to about 81% in the dual index therapy group.

Table 4.3 Demographic Characteristics by Index Drug Type

Demographic characteristics by Index Drug Type	***Hydroxyurea Users* N=153**	***Opioid Users* N=1,069**	***Non-opioid Users* N=855**	***Dual Therapy Users*** [a] **N=262**
Age at index date				
Mean ± SD, years	**14.1 ± 11.9**	**22.3 ± 15.3**	**15.5 ± 14.2**	**20.9 ± 10.7**
Age groups, N (col %)				
2-12, 965 (41.3%)	88 (57.5)	353 (33.0)	465 (54.4)	59 (22.5)
13-17, 272 (11.6%)	19 (12.4)	112 (10.5)	112 (13.1)	29 (11.1)
18-25, 375 (16.0%)	21 (13.7)	180 (16.8)	85 (10.0)	89 (34.0)
26-40, 483 (20.7%)	18 (11.8)	265 (24.8)	124 (14.5)	76 (29.0)
41-63, 244 (10.4%)	7 (4.6)	159 (14.9)	69 (8.1)	9 (3.4)
Total	153 (100.0)	1,069 (100.0)	855 (100.1) [b]	262 (100.0)
***Gender,* N (%)**				
Female	77 (50.3)	649 (60.7)	524 (61.3)	211 (80.5)
Male	76 (49.7)	420 (39.3)	331 (38.7)	51 (19.5)
Total	153 (100.0)	1,069 (100.0)	855 (100.0)	262 (100.0)

[a] Dual therapy users received both opioid and non-opioid analgesics on their index date
[b] Total does not equal to 100.0% due to rounding.

4.3.2 Objective 2: Index Drug Category by Age Group

Objective 2 aimed at determining if there were differences in the type of SCD index therapy by age group among the study sample. An omnibus chi-square test showed that there is a

significant difference in the type of SCD index therapy by age group (χ^2 = 243.0, p<0.0001) as shown in Tables 4.4 and 4.4a.

Table 4.4 Chi-square Analysis for Index Drug Category by Age Group

Index Drug Category	Age Group					All patients (N=2,339)
	2-12 N (col %)	13-17 N (col %)	18-25 N (col %)	26-40 N (col %)	41-63 N (col %)	
Hydroxyurea	88 (9.1)	19 (7.0)	21 (5.6)	18 (3.7)	7 (2.9)	153 (6.5%)
Opioids	353 (36.6)	112 (41.2)	180 (48.0)	265 (54.9)	159 (65.2)	1,069 (45.7%)
Non-opioids	465 (48.2)	112 (41.2)	85 (22.7)	124 (25.7)	69 (28.3)	855 (36.6%)
Dual therapy	59 (6.1)	29 (10.7)	89 (23.7)	76 (15.7)	9 (3.7)	262 (11.2%)
Total	965 (100.0)	272 (100.1) [a]	375 (100.0)	483 (100.0)	244 (100.1) [a]	2,339 (100.0%)

χ^2 = 243.0, df=12, p <0.0001

[a] Total does not equal to 100.0% due to rounding.

Table 4.4a P-values[a] of Pairwise Chi-square Comparisons Between Index Drug Category vs. Age Group

Pairwise Age Group	Hydroxyurea	Opioids	Non-opioids	Dual therapy
2-12 vs. 13-17	0.2688	0.1669	0.0407	0.0100
2-12 vs. 18-25	0.0344	0.0001	<0.0001	<0.0001
2-12 vs. 26-40	0.0002	<0.0001	<0.0001	<0.0001
2-12 vs. 41-63	0.0012	<0.0001	<0.0001	0.1418
13-17 vs. 18-25	0.4702	0.0851	<0.0001	<0.0001
13-17 vs. 26-40	0.0465	0.0003	<0.0001	0.0531
13-17 vs. 41-63	0.0328	<0.0001	0.0022	0.0025
18-25 vs. 26-40	0.1913	0.0459	0.3089	0.0032
18-25 vs. 41-63	0.1101	<0.0001	0.1145	<0.0001
26-40 vs. 41-63	0.5489	0.0078	0.4525	<0.0001

[a] α-level of 0.00125 used for pairwise chi-square comparisons to maintain family-wise type I error rate at ≤ 0.05

Shaded p-values indicate significance at p<0.00125

Hydroxyurea

Following the chi-square test, 40 pairwise chi-square comparisons were performed to investigate which age groups significantly differed from other age groups within each index drug category. On conducting post-hoc pairwise comparisons using an α-level of 0.00125, the proportion of patients using hydroxyurea as index therapy differed significantly by age group (Tables 4.4 and 4.4a). The proportion of patients using hydroxyurea as index therapy was significantly higher for age group 2-12 (9.1%) as compared to age groups 26-40 (3.7%, p= 0.0002) and 41-63 (2.9%, p= 0.0012). However, proportions of patients using hydroxyurea as index therapy were comparable among age groups 2-12, 13-17 and 18-25 (p>0.00125). The proportions of patients using hydroxyurea as index therapy were also comparable among age groups 13-17, 18-25, 26-40, and 41-63 (p>0.00125). Because the overall omnibus test was significant, the following hypothesis was not rejected:

> *H_{2A}: The proportion of patients using HU as index therapy decreases significantly with an increase in age groups.* ***(Failed to Reject)***

Opioids

After conducting post-hoc pairwise chi-square comparisons using an α-level of 0.00125, the proportion of patients using opioid analgesics as index therapy differed significantly by age groups. The proportion of patients using opioids as index therapy was significantly lower for age group 2-12 (36.6%) as compared to age groups 18-25 (48.0%, p=0.0001), 26-40 (54.9%, p<0.0001), and 41-63 (65.2%, p<0.0001). Furthermore, the proportion of patients using opioids as index therapy was significantly lower for age group 13-17 (41.2%) as compared to age groups 26-40 (54.9%, p= 0.0003) and 41-63 (65.2%, p<0.0001). The proportion of patients using opioids as index therapy was significantly lower for age group 18-25 (48.0%) as compared to age group 41-

63 (65.2%, p<0.0001). Finally, the proportions of patients using opioids as index therapy were comparable among age groups 2-12 and 13-17, 13-17 and 18-25, 18-25 and 26-40, and 26-40 and 41-63 (p>0.00125) (Tables 4.4 and 4.4a). Because the overall omnibus test was significant, the following hypothesis was not rejected:

H_{2B}: The proportion of patients using opioid analgesics as index therapy increases significantly with an increase in age groups. ***(Failed to Reject)***

Non-opioids

Pairwise chi-square comparisons among index non-opioid analgesic users revealed that there was a significant difference in proportion of patients using non-opioid analgesics as index therapy among various age groups (Tables 4.4 and 4.4a). Using an α-level of 0.00125, the proportion of patients using non-opioids as index therapy was significantly higher for age group 2-12 (48.2%) as compared to age groups 18-25 (22.7%, p<0.0001), 26-40 (25.7%, p<0.0001) and 41-63 (28.3%, p<0.0001). Moreover, the proportion of patients using non-opioids as index therapy was significantly higher for age group 13-17 (41.2%) as compared to age groups 18-25 (22.7%, p<0.0001) and 26-40 (25.7%, p<0.0001). Finally, the proportions of patients using non-opioids as index therapy were comparable among age groups 2-12 and 13-17 (p>0.00125) and age groups 13-17 and 41-63 (p>0.00125). The proportions of patients using non-opioids as index therapy were also comparable among age groups 18-25, 26-40, and 41-63 (p>0.00125). Because the overall omnibus test was significant, the following hypothesis was rejected:

*Ho_{2C}: There is no significant difference in proportion of patients using non-opioid analgesics as index therapy among various age groups. (**Rejected**)*

Dual Therapy

After conducting post-hoc pairwise chi-square comparisons using a α-level of 0.00125, there was significant difference in the proportion of patients using dual index therapy among age groups as shown in Tables 4.4 and 4.4a. The proportion of patients using dual index therapy was significantly lower for age group 2-12 (6.1%) as compared to age groups 18-25 (23.7%, $p<0.0001$) and 26-40 (15.7%, $p<0.0001$). The proportion of patients using dual index therapy was also significantly lower for age group 13-17 (10.7%) as compared to age group 18-25 (23.7%, $p<0.0001$). The proportion of patients using dual index therapy was significantly lower for age group 41-63 (3.7%) as compared to age groups 18-25 (23.7%, $p<0.0001$) and 26-40 (15.7%, $p<0.0001$). However, the proportions of patients using dual index therapy were comparable among age groups 2-12, 13-17, and 41-63. The proportion of patients using dual index therapy was also comparable among age groups 13-17, 26-40, and 41-63. Finally, the proportion of patients using dual index therapy was comparable among age groups 18-25 and 26-40. Because the overall omnibus test was significant, the following hypothesis was not rejected:

> *H_{2D}: The proportion of patients using dual drugs as index therapy increases significantly with an increase in age groups.* ***(Failed to Reject)***

4.3.3 Objective 3: Medication Utilization by Age Group

Objective 3 aimed at determining if there were differences in the medication utilization of SCD-related drugs (hydroxyurea, opioid and non-opioid analgesics) by age group.

4.3.3.1 Hydroxyurea adherence by age group

First, utilization of HU was evaluated in terms of adherence to HU since this drug is recommended to be taken on a chronic basis. Adherence of HU, measured using the medication

possession ratio (MPR), was compared among different age groups to determine if HU adherence varied significantly among age groups. Moreover, adherence to HU was measured among HU index users who received HU as the first SCD drug during the identification period as well as all HU users who received HU during identification period regardless of whether HU was their index drug. For HU index users, the ANOVA conducted between MPR and age group revealed that adherence to HU index prescriptions differed significantly by age groups [F (4, 148) =7.5, p<0.0001]. For all HU users, ANOVA revealed that adherence differed significantly by age groups [F (4, 426) =22.1, p<0.0001] (Table 4.5).

Table 4.5 ANOVA Comparison of Hydroxyurea Adherence by Age Group [Index users (N=153); All hydroxyurea users (N=431)]

	Mean Hydroxyurea Adherence (MPR)			
	Hydroxyurea Index Users (N= 153)		All Hydroxyurea Users (N= 431)	
Age groups	**N**	**Mean (SD)**	**N**	**Mean (SD)**
2 to 12	88	65.2 (28.3) [a]	233	58.9 (30.7) [c]
13 to 17	19	47.2 (27.6) [a, b]	49	43.7 (27.8) [d]
18 to 25	21	37.2 (27.2) [b]	73	29.5 (23.1) [e]
26 to 40	18	34.7 (31.1) [b]	53	32.0 (28.0) [d, e]
41 to 63	7	52.6 (32.3) [a, b]	23	31.9 (27.3) [d, e]
ANOVA results	F (df: 4, 148) =7.5, p<0.0001		F (df: 4, 426) =22.1, p<0.0001	

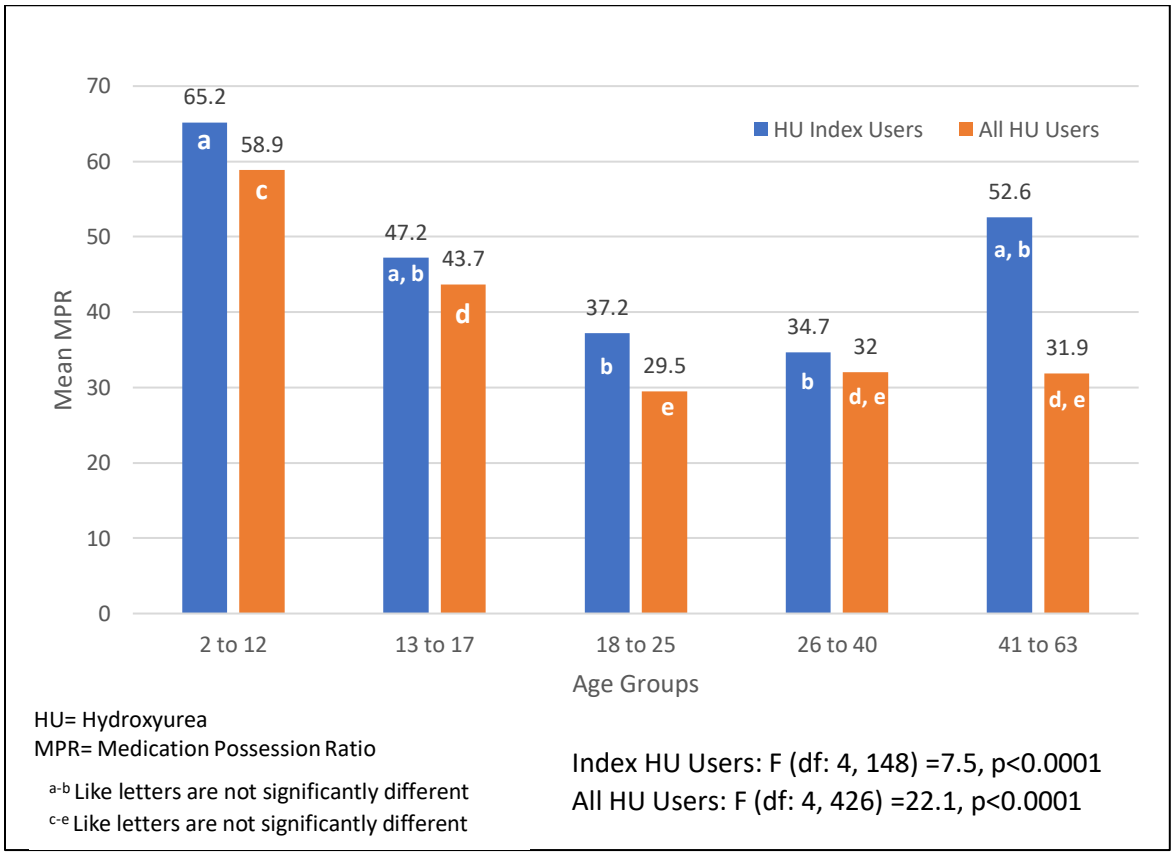
ANOVA= Analysis of Variance
MPR=Medication Possession Ratio
Hydroxyurea index users refer to patients who were prescribed hydroxyurea as their index drug.
All hydroxyurea users refer to patients who were prescribed hydroxyurea at any point during the follow-up period, regardless of their index drug type.
[a-b] Duncan's post-hoc: Within each group (hydroxyurea index users), like letters are not significantly different.
[c-e] Duncan's post-hoc: Within each group (all hydroxyurea users), like letters are not significantly different.

Duncan's post-hoc analysis was conducted to identify which age groups differed from others. Duncan's post-hoc analysis revealed that HU (index) adherence among patients of age group 2-12 (65.2% ± 28.3%) was significantly ($p<0.05$) higher than HU adherence among patients of age groups 18-25 (37.2% ± 27.2%) and 26-40 (34.7% ± 31.1%). On the other hand, HU adherence was comparable among patients of age groups 2-12 (65.2% ± 28.3%), 13-17 (47.2% ± 27.6%), and 41-63 (52.6% ± 32.3%) with p-values > 0.05. HU adherence was comparable among age groups 13-17 (47.2% ± 27.6%), 18-25 (37.2% ± 27.2%), 26-40 (34.7% ± 31.1%), and 41-63 (52.6% ± 32.2%) with p-values > 0.05 (Table 4.5, Figure 4.1).

As adherence to all HU prescriptions was found to be significantly different among patients of different age groups, Duncan's post-hoc analysis was conducted to identify which age groups differed from others. Duncan's post-hoc analysis revealed that HU adherence among patients of age group 2-12 (58.9% ± 30.7%) was significantly ($p<0.05$) higher than HU adherence among patients of all other age groups 13-17 (43.7% ± 27.8%), 18-25 (29.5% ± 23.1%), 26-40 (32.0% ± 28.0%), and 41-63 (31.9% ± 27.3%). Furthermore, HU adherence among patients of age group 13-17 (43.7% ± 27.8%) was significantly higher than HU adherence among patients of age group 18-25 (29.5% ± 23.1%). However, HU adherence was comparable among patients of age groups 13-17 (43.7% ± 27.8%), 26-40 (32.0% ± 28.0%), and 41-63 (31.9% ± 27.3%) with p-values >0.05. Finally, HU adherence was comparable among patients of age groups 18-25 (29.5% ± 23.1%), 26-40 (32.0% ± 28.0%), and 41-63 (31.9% ± 27.3%) with p-values >0.05 (Table 4.5, Figure 4.1). Because the overall omnibus test was significant, the following hypothesis was not rejected:

H_{3A}: Adherence to HU decreases significantly with an increase in age group. ***(Failed to Reject)***

Figure 4.1 Mean Hydroxyurea Adherence by Age Group [Index users (N=153); All hydroxyurea users (N=431)]



4.3.3.2 Opioid analgesic utilization by age group

Utilization of SCD-related opioid analgesics was evaluated in terms of mean total days' supply since they are used on an as needed basis. Mean total days' supply for SCD-related opioid analgesics, calculated as the sum of total days' supply for all fills within the observation period (365 days), was compared among different age groups to determine if opioid analgesic utilization varied significantly among age groups. Moreover, mean total days' supply of opioid analgesics was measured among opioid index users who received opioid analgesics as first SCD drug during identification period as well as all opioid users who received opioid analgesics during

identification period regardless of whether opioid was their index drug. Since the total days' supply of opioid analgesics was not normally distributed, a Kruskal-Wallis test was conducted between total days' supply and age group.

For opioid index users, the Kruskal-Wallis test revealed that total days' supply of opioid index prescriptions differed significantly by age groups [χ^2(df:4) =211.3, p<0.0001]. For all opioid users, the Kruskal-Wallis test revealed that total days' supply of all opioid prescriptions differed significantly by age groups [χ^2=300.8, p<0.0001] (Table 4.6).

Table 4.6 Kruskal-Wallis Comparison of Annual Total Days Supply: Opioids by Age Group [Index opioid users (N=1,069); All opioid users (N=1,780)]

	Mean[a] Annual Total Days' Supply: Opioids			
	Opioid Index Users (N=1,069)		**All Opioid Users (N=1,780)**	
Age groups	**N**	**Mean (SD) (Median)**	**N**	**Mean (SD) (Median)**
2 to 12	353	13.0 (15.0) [b] (8.0)	570	13.0 (14.6) [f] (8.0)
13 to 17	112	17.2 (32.5) [b] (8.0)	205	15.0 (30.4) [f] (6.0)
18 to 25	180	56.2 (111.3) [c] (10.5)	340	38.1 (86.9) [f] (8.0)
26 to 40	265	86.0 (138.3) [d] (26.0)	443	66.0 (121.8) [g] (17.0)
41 to 63	159	158.8 (180.8) [e] (86.0)	222	143.6 (171.8) [h] (65.5)
Kruskal-Wallis results	χ^2(df:4) =211.3, p<0.0001		χ^2(df:4) =300.8, p<0.0001	

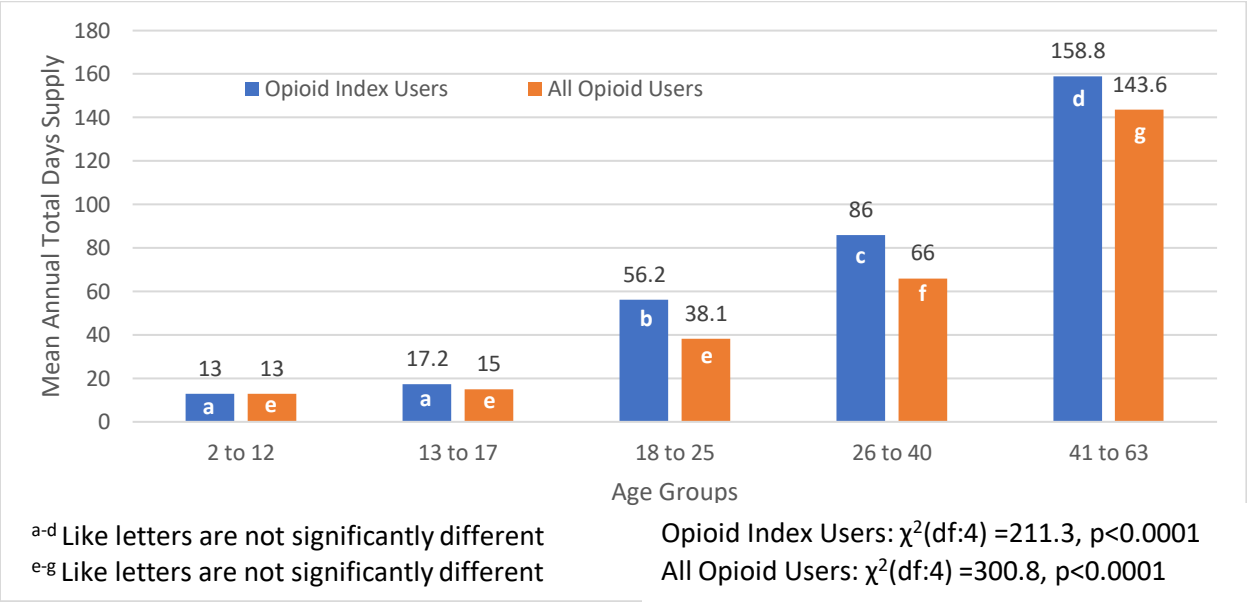
Opioid index users refer to patients who were prescribed opioids as their index drug.
All opioid users refer to patients who were prescribed opioids at any point during the follow-up period, regardless of their index drug type.
[a] Although a Kruskal Wallis test was used, mean (sd) values are shown in the table for ease of interpretation. Pairwise multiple comparisons conducted using Dwass, Steel, Critchlow-Fligner (DSCF) method using α=0.005.
[b-e] Within each group (opioid index users), like letters are not significantly different.
[f-h] Within each group (all opioid users), like letters are not significantly different.

As total days' supply of opioid index prescriptions was found to be significantly different among patients of different age groups, multiple pairwise comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as post-hoc analyses to identify which groups significantly differed from other groups. The post-hoc test revealed that all pairwise comparisons were significantly ($p<0.005$) different except the comparison between age groups 2-12 and 13-17 ($p>0.05$). Total days' supply of opioid index prescriptions was lowest among groups 2-12 (13.0 ± 15.0) and 13-17 (17.2 ± 32.5), followed by age group 18-25 (56.2 ± 111.3), and 26-40 (86.0 ± 138.3,), and then highest among patients of age group 41-63 (158.8 ± 180.8) (Table 4.6, Figure 4.2).

In addition, as total days' supply of all opioid prescriptions was significantly different among patients of different age groups, multiple pairwise comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as a post-hoc analysis to identify which groups significantly differed from other groups. The post-hoc test revealed that total days' supply of all opioid index prescriptions was lowest among groups 2-12 (13.0 ± 14.6), 13-17 (15.0 ± 30.4), and 18-25 (38.1 ± 86.9), followed by age group 26-40 (66.0 ± 121.8), and then highest among patients of age group 41-63 (143.6 ± 171.8). Total days' supply of all opioid prescriptions was comparable among patients of age groups 2-12 (13.0 ± 14.6), 13-17 (15.0 ± 30.4), and 18-25 (38.1 ± 86.9) (Table 4.6, Figure 4.2). Because the overall omnibus test was significant, the following hypothesis was not rejected:

*H_{3B}: The mean total days' supply of opioid analgesics increases significantly with an increase in age groups. (**Failed to Reject**)*

Figure 4.2 Mean Annual Total Days' Supply: Opioids by Age Group [Index opioid users (N=1,069); All opioid users (N=1,780)]



4.3.3.3 Non-opioid analgesic utilization by age group

Utilization of SCD-related non-opioid analgesics was evaluated in terms of mean total days' supply since they are used on an as needed basis. Mean total days' supply for SCD-related non-opioid analgesics, calculated as the sum of total days' supply for all fills within the observation period (365 days), was compared among different age groups to determine if non-opioid analgesic utilization varied significantly among age groups. Moreover, mean total days' supply of non-opioid analgesics was measured among non-opioid index users who received non-opioid analgesics as first SCD drug during identification period as well as all non-opioid users who received non-opioid analgesics during identification period regardless of whether non-opioid was their index drug. Since the total days' supply of non-opioid analgesics was non-parametric data, a Kruskal-Wallis test was conducted between total days' supply and age group.

For non-opioid index users, total days' supply of non-opioid index prescriptions differed significantly by age groups [χ^2(df:4) =161.1, p<0.0001]. For all non-opioid users, total days' supply of all non-opioid prescriptions differed significantly by age groups [χ^2(df:4) =271.2, p<0.0001] (Table 4.7).

Table 4.7 Kruskal-Wallis Comparison of Annual Total Days Supply: Non-opioids by Age Group [Index non-opioid users (N=855); All non-opioid users (N=1,738)]

	Mean[a] Annual Total Days Supply: Non-opioids			
	Non-opioid Index Users (N=855)		**All Non-opioid Users (N=1,738)**	
Age groups	**N**	**Mean (SD) (Median)**	**N**	**Mean (SD) (Median)**
2 to 12	465	14.8 (17.0) [b] (10.0)	729	16.3 (18.5) [e] (10.0)
13 to 17	112	33.2 (41.0) [c] (19.5)	210	29.8 (35.4) [f, g] (16.5)
18 to 25	85	26.1 (39.3) [c] (15.0)	279	23.9 (35.8) [f] (15.0)
26 to 40	124	41.5 (57.5) [c] (23.0)	360	38.3 (49.5) [g] (21.5)
41 to 63	69	133.6 (138.4) [d] (80.0)	160	105.2 (117.6) [h] (60.0)
Kruskal-Wallis results	χ^2(df:4) =161.1, p<0.0001		χ^2(df:4) =271.2, p<0.0001	

Non-opioid index users refer to patients who were prescribed non-opioids as their index drug.
All non-opioid users refer to patients who were prescribed non-opioids at any point during the follow-up period, regardless of their index drug type.
[a] Although a Kruskal Wallis test was used, mean (sd) values are shown in the table for ease of interpretation. Pairwise multiple comparisons conducted using Dwass, Steel, Critchlow-Fligner (DSCF) method using α=0.005.
[b-d] Within each group (non-opioid index users), like letters are not significantly different.
[e-h] Within each group (all non-opioid users), like letters are not significantly different.

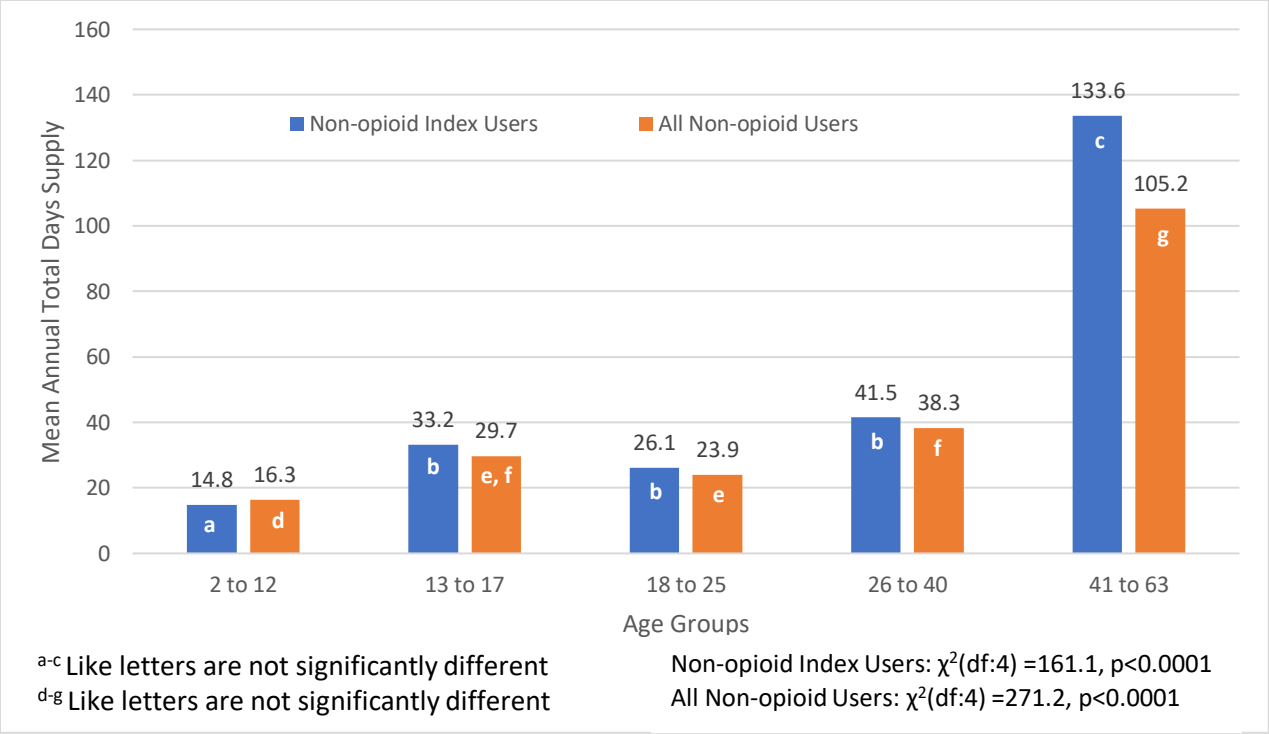
As the total days' supply of non-opioid index prescriptions was significantly different among patients of different age groups, multiple pairwise comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as a post-hoc analysis to identify which groups significantly ($p<0.005$) differed from other groups. The post-hoc test showed that total days' supply of non-opioid index prescriptions was lowest among group 2-12 (14.8 ± 17.0) as compared to all other age groups 13-17 (33.2 ± 41.0), 18-25 (26.1 ± 39.3), 26-40 (41.5 ± 57.5), and 41-63 (133.6 ± 138.4). Total days' supply of non-opioid index prescriptions was significantly higher among age group 41-63 (133.6 ± 138.4) as compared to age groups 13-17 (33.2 ± 41.0), 18-25 (26.1 ± 39.3), and 26-40 (41.5 ± 57.5). Finally, total days' supply of non-opioid index prescriptions was comparable among patients of age groups 13-17 (33.2 ± 41.0), 18-25 (26.1 ± 39.3) and 26-40 (41.5 ± 57.5) with p-values >0.005 (Table 4.7, Figure 4.3).

Among all non-opioid analgesic users, as the total days' supply of all non-opioid prescriptions was found to be significantly different among patients of different age groups, multiple pairwise comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as post-hoc analysis to identify which groups significantly differed from other groups. The post-hoc test showed that total days' supply of all non-opioid prescriptions was lowest among group 2-12 (16.3 ± 18.5) as compared to all other age groups 13-17 (29.8 ± 35.4, $p<0.0001$), 18-25 (23.9 ± 35.8, $p<0.0001$), 26-40 (38.3 ± 49.5, $p<0.0001$), and 41-63 (105.2 ± 117.6, $p <0.0001$). In addition, total days' supply of all non-opioid prescriptions was significantly higher among age group 41-63 (105.2 ± 117.6) as compared to age groups 13-17 (29.8 ± 35.4, $p<0.0001$), 18-25 (23.9 ± 35.8, $p<0.0001$), and 26-40 (38.3 ± 49.5, $p<0.0001$). Total days' supply of all non-opioid prescriptions was also significantly higher among age group 26-40 (38.3 ± 49.5) as compared to age group 18-25 (23.9 ± 35.8, $p=0.0002$). Finally, total days' supply of all non-opioid prescriptions was

comparable among patients of age groups 13-17 (29.8 ± 35.4) and 18-25 (23.9 ± 35.8), and among patients of age groups 13-17 (29.8 ± 35.4) and 26-40 (38.3 ± 49.5) with p-values > 0.005 (Figure 4.3). Because the overall omnibus test was significant, the following hypothesis was not rejected:

H_{3C}: The mean total days' supply of non-opioid analgesics increases significantly with an increase in age groups. ***(Failed to Reject)***

Figure 4.3 Mean Annual Total Days Supply: Non-opioids by Age Group [Index non-opioid users (N=855); All non-opioid users (N=1,738)]



4.3.4 Objective 4: Healthcare Service Utilization by Age Group

Objective 4 aimed at determining if there were differences in SCD-related healthcare service utilization (ED, inpatient, and outpatient visits, all-cause prescription drugs) by age group among the study sample.

4.3.4.1 Emergency department utilization by age group

A chi-square test was used to determine if the proportion of patients with one or more SCD-related emergency department visits differed significantly among age groups. Out of the total 2,339 patients, 1,636 (69.9%) patients did not have any SCD-related emergency department visits during the 12-month follow-up period. However, 703 (30.1%) patients had one or more SCD-related emergency department visits during the 12-month follow-up period. As shown in Table 4.8, a chi-square test revealed that the proportion of patients with one or more SCD-related emergency department visits differed significantly by age groups [χ^2(df:4) =19.5, p<0.001].

Furthermore, multiple pairwise chi-square comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as post-hoc analysis to identify which groups significantly differed from other groups. As shown in Table 4.8, the post-hoc test showed that the proportion of patients with one or more SCD-related ED visits was statistically significantly higher for age groups 2-12 (33.2%) and 26-40 (32.3%) as compared to age group 13-17 (21.3%). On the other hand, proportions of patients with one or more SCD-related ED visits were comparable among age groups 2-12 (33.2%), 18-25 (29.3%), 26-40 (32.3%), and 41-63 (24.2%). Moreover, the proportions of patients with one or more SCD-related ED visits were also comparable among age groups 13-17 (21.3%), 18-25 (29.3%), and 41-63 (24.2%) (Table 4.8). Because the overall omnibus test was significant, the following hypothesis was not rejected.

*H_{4A}: The proportion of patients with one or more SCD-related emergency department visits increases significantly with an increase in age groups. (**Failed to Reject**)*

Table 4.8 Chi-square Analysis for SCD-related Emergency Department Visits by Age Group (N=2,339)

SCD-related Emergency Department Visits	Age Group					
	2-12 N (col %)	13-17 N (col %)	18-25 N (col %)	26-40 N (col %)	41-63 N (col %)	Total
Proportion of patients with one or more ED visits	320 (33.2) [a]	58 (21.3) [b,c]	110 (29.3) [a, c]	156 (32.3) [a]	59 (24.2) [a,c]	703
Proportion of patients with no ED visits	645 (66.8)	214 (78.7)	265 (70.7)	327 (67.7)	185 (75.8)	1,636
Total	965 (100.0)	272 (100.0)	375 (100.0)	483 (100.0)	244 (100.0)	2,339

χ^2 =19.5, df=4, p <.001

[a-c] Like letters are not significantly different as per multiple pairwise comparisons using α-level=0.005 (10 comparisons)

4.3.4.2 Inpatient hospital utilization by age group

To assess hospital utilization among the study sample, chi-square test was used to determine if proportion of patients with one or more SCD-related hospital admissions differed significantly among different age groups. Out of the total 2,339 patients, 1,836 (78.5%) patients did not have any SCD-related hospital admissions during the 12-month follow-up period. However, 503 (21.5%) patients had one or more SCD-related hospital admissions during the 12-month follow-up period. As shown in Table 4.9, chi-square test revealed that the proportion of

patients with one or more SCD-related hospital admissions differs significantly by age groups [χ^2(df:4) =18.1, p<0.05].

Furthermore, multiple pairwise post-hoc comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted to determine if any group differed significantly from other groups. As shown in Table 4.9, the post-hoc test showed that proportion of patients with one or more SCD-related hospital admission was statistically significantly lower for age groups 13-17 (12.9%) as compared to age groups 2-12 (23.0%), 18-25 (25.1%), and 26-40 (22.4%). In addition, the proportion of patients with one or more SCD-related hospital admission was comparable among age groups 13-17 (12.9%) and 41-63 (18.0%). The proportions of patients with one or more SCD-related hospital admission were also comparable among age groups 2-12 (23.0%), 18-25 (25.1%), 26-40 (22.4%), and 41-63 (18.0%) (Table 4.9). Because the overall omnibus test was significant, the following hypothesis was not rejected.

H_{4B}: The proportion of patients with one or more SCD-related hospital admission increases significantly with an increase in age groups. ***(Failed to Reject)***

Table 4.9 Chi-square Analysis for SCD-related Hospital Admission by Age Group (N=2,339)

SCD-related hospital admission	Age Group					
	2-12 N (col %)	13-17 N (col %)	18-25 N (col %)	26-40 N (col %)	41-63 N (col %)	Total
Proportion of patients with one or more hospital admission	222 (23.0) [a]	35 (12.9) [b]	94 (25.1) [a]	108 (22.4) [a]	44 (18.0) [a, b]	503
Proportion of patients with no hospital admission	743 (77.0)	237 (87.1)	281 (74.9)	375 (77.6)	200 (82.0)	1,836
Total	965 (100.0)	272 (100.0)	375 (100.0)	483 (100.0)	244 (100.0)	2,339

χ^2 =18.1, df=4, p <0.05

[a-b] Like letters are not significantly different as per multiple pairwise comparisons using α-level=0.005 (10 comparisons)

4.3.4.3 Outpatient visits utilization by age group

To assess utilization of outpatient visits among the study sample, number of SCD-related outpatient visits were compared among patients of different age groups. As the number of outpatient visits was not normally distributed, a Kruskal-Wallis test was performed which revealed that the number of outpatient visits differed significantly by age groups [χ^2=58.2, p<0.0001]. Following the omnibus test, multiple pairwise comparisons (α-level=0.005 for 10 pairwise comparisons) were conducted as post-hoc analysis to identify which groups significantly differed from other groups. As shown in Table 4.10, the post-hoc test showed that number of SCD-related outpatient visits was highest among age group 2-12 (4.5 ± 7.6) as compared to all other age groups 13-17 (2.9 ± 5.4), 18-25 (3.6 ± 8.4), 26-40 (4.3 ± 10.6), and 41-63 (3.9 ± 8.9). However, total

number of SCD-related outpatient visits were comparable among patients of age groups 13-17 (2.9 ± 5.4), 18-25 (3.6 ± 8.4), 26-40 (4.3 ± 10.6), and 41-63 (3.9 ± 8.9) (Table 4.10). Because the overall omnibus test was significant, the following hypothesis was not rejected.

H_{4C}: The number of SCD-related outpatient visits increases significantly with increase in age groups. ***(Failed to Reject)***

Table 4.10 Kruskal-Wallis Comparison of Number of SCD-related Outpatient Visits by Age Group (N=2,339)

	Mean[a] Number of SCD-related Outpatient Visits	
Age groups	**N**	**Mean (SD) (Median)**
2 to 12	965	4.5 (7.6) [b] (1.0)
13 to 17	272	2.9 (5.4) [c] (0.0)
18 to 25	375	3.6 (8.4) [c] (0.0)
26 to 40	483	4.3 (10.6) [c] (0.0)
41 to 63	244	3.9 (8.9) [c] (0.0)
Kruskal-Wallis results	χ^2(df:4) =58.2, p<0.0001	

[a] Although a Kruskal-Wallis test was used, mean (sd) values are shown in the table for ease of interpretation. Pairwise multiple comparisons conducted using Dwass, Steel, Critchlow-Fligner (DSCF) method using α=0.005.
[b-c] Like letters are not significantly different.

4.3.4.4 All-cause prescription medication utilization by age group

To assess all-cause prescription drug utilization among the study sample, mean total number of all-cause prescription medications were compared among patients of different age groups. As the number of all-cause prescription medications was normally distributed, ANOVA

was performed which revealed that the mean number of all-cause prescription medications differed significantly by age groups F (4, 2334) =37.4, p<0.0001]. Following the omnibus-test, Duncan's post-hoc analysis (α-level=0.005 for 10 pairwise comparisons) was conducted to identify which groups significantly differed from other groups. As shown in Table 4.11, the post-hoc test showed that mean total number of all-cause prescription medications were comparable among patients of age groups 2-12 (13.7 ± 9.9) and 26-40 (14.8 ± 13.2), and age groups 13-17 (11.8 ± 9.8) and 18-25 (11.9 ± 10.8). The mean number of all-cause prescription medications of age group 41-63 years (22.4 ± 16.3) was significantly higher than that of all other age groups. The mean total number of all-cause prescription drugs was highest among patients of age group 41-63 (22.4 ± 16.3), followed by age groups 2-12 (13.7 ± 9.9) and 26-40 (14.8 ± 13.2), and then lowest among age groups 13-17 (11.8 ± 9.8) and 18-25 (11.9 ± 10.8) (Table 4.11). Because the overall omnibus test was significant, the following hypothesis was not rejected.

H_{4D}: The mean number of all-cause prescription medications increases with increase in age groups. ***(Failed to Reject)***

Table 4.11 ANOVA Comparison of Number of All-cause Prescription Medications by Age Group (N=2,339)

Age groups	Mean Number of All-cause Prescription Drug	
	N	Mean (SD)
2 to 12	965	13.7 (9.9) [a]
13 to 17	272	11.8 (9.8) [b]
18 to 25	375	11.9 (10.8) [b]
26 to 40	483	14.8 (13.2) [a]
41 to 63	244	22.4 (16.3) [c]
ANOVA results	F (4, 2334) =37.4, p<0.0001	

ANOVA= Analysis of Variance

[a-c] Like letters are not significantly different. Duncan's post-hoc test was used.

4.3.5 Objective 5: Temporal Use of Healthcare Services after an ED Visit or Hospitalization

Objective 5 was an exploratory objective to describe the temporal patterns of use of healthcare services in SCD. From the study sample of 2,339 patients, 801 patients, who had either an ED visit or inpatient hospitalization, were followed from the date of first ED or inpatient visit until the end of 12-month post-index follow-up period. Hence, these patients were followed for varying lengths of time. As shown in Table 4.12, out of these 801 patients, 598 (74.7%) had an ED visit as the index healthcare service, while 203 (25.3%) patients had an inpatient admission/hospitalization as the index healthcare service.

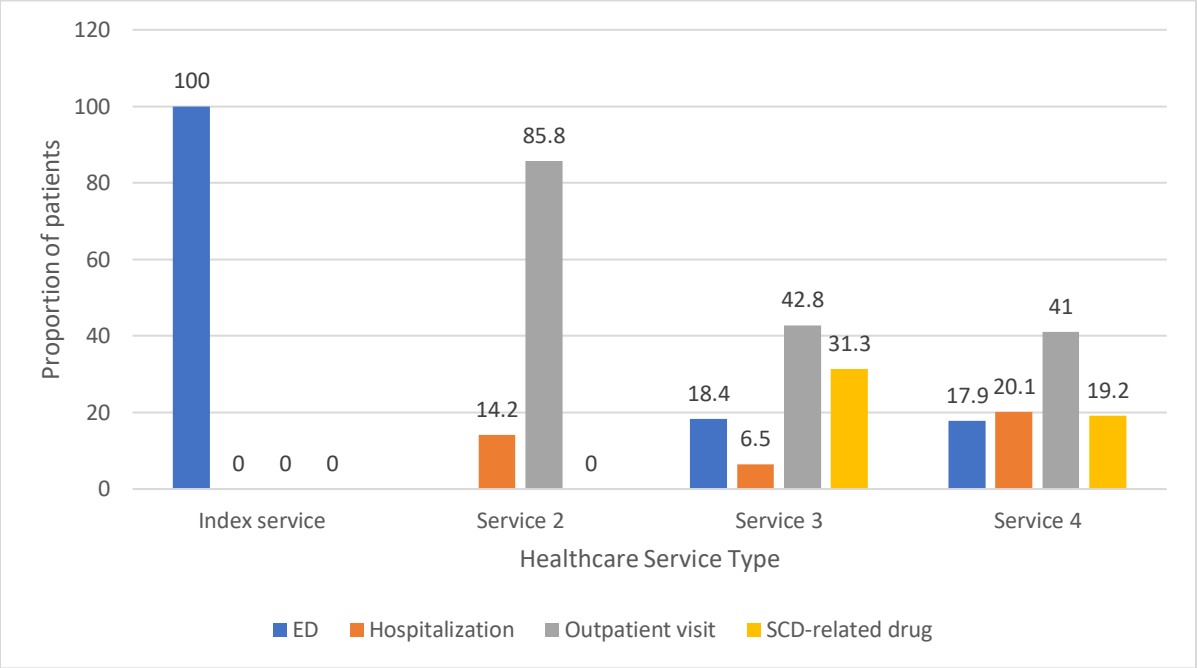
Table 4.12 Temporal Use of Healthcare Services after an ED visit or Hospitalization (N=801)

		Proportion of patients receiving healthcare service N (%)		
INDEX SERVICE TYPE (Service 1)	**Subsequent Healthcare Service type**	**Service 2**	**Service 3**	**Service 4**
ED (N=598; 74.7%)	*ED*	0 (0.0)	110 (18.4)	107 (17.9)
	Hospitalization	85 (14.2)	39 (6.5)	120 (20.1)
	Outpatient visit	513 (85.8)	256 (42.8)	245 (41.0)
	SCD-related drug	0 (0.0)	187 (31.3)	115 (19.2)
	No service	0 (0.0)	6 (1.0)	11 (1.8)
HOSPITALIZATION (N=203; 25.3%)	*ED*	16 (7.9)	7 (3.4)	16 (7.9)
	Hospitalization	87 (42.8)	108 (53.2)	78 (38.4)
	Outpatient visit	72 (35.5)	56 (27.6)	62 (30.5)
	SCD-related drug	26 (12.8)	28 (13.8)	39 (19.2)
	No service	2 (1.0)	4 (2.0)	8 (3.9)

ED= Emergency department, SCD= Sickle cell disease

Among the 598 patients with ED visits as an index service, 85 (14.2%) patients were hospitalized, while 513 (85.8%) had an outpatient visit after their index ED visit. After these services, 110 (18.4%) patients had subsequent ED visits, while 39 (6.5%), 256 (42.8%), and 187 (31.3%) patients had a hospitalization, outpatient visits, and SCD-related prescription drug, respectively (Figure 4.4). A pattern was observed that if patients had index ED visits, they also had significant number of subsequent outpatient visits in future.

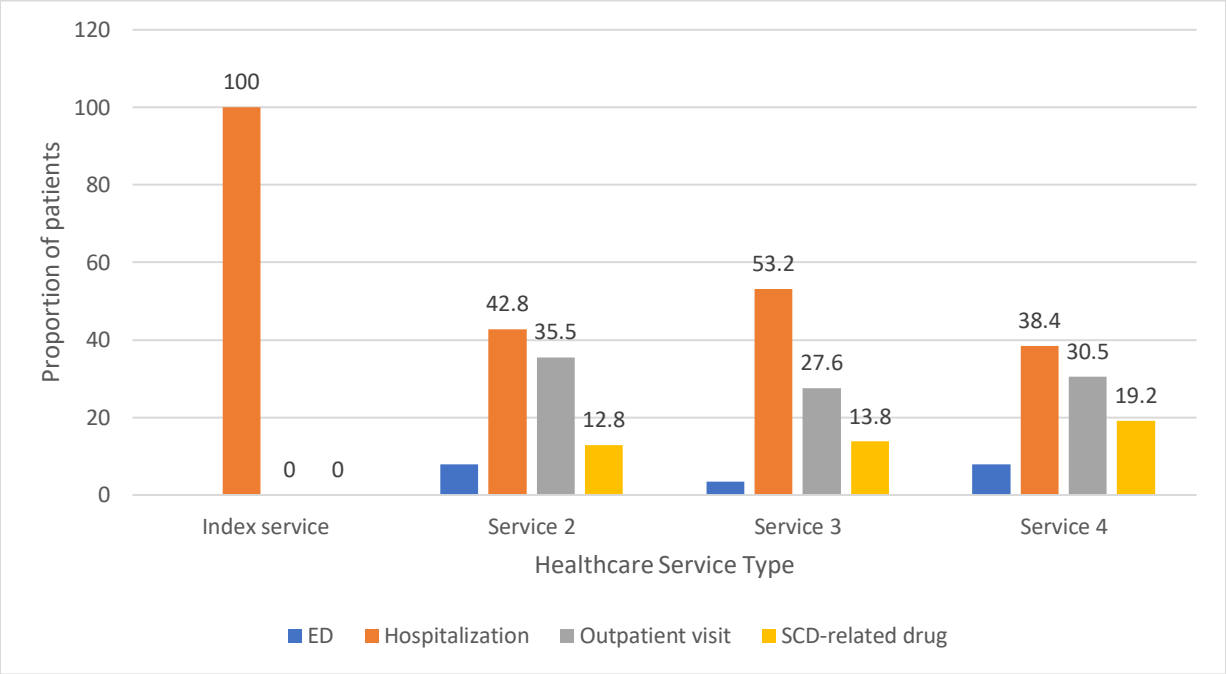
Figure 4.4 Temporal Use of Healthcare Services after an ED Visit (N=598)



ED= Emergency department, SCD= Sickle cell disease

Among the 203 patients with hospitalization as index service, 16 (7.9%), 87 (42.8%), 72 (35.5%), and 26 (12.8%) patients had an ED visit, hospitalization, outpatient visit, and SCD-related prescription drug, respectively, as subsequent healthcare services. After these services, 7 (3.4%), 108 (53.2%), 56 (27.6%), and 28 (13.8%) patients had subsequent ED visits, hospitalization, outpatient visits, and SCD-related prescription drug, respectively (Figure 4.5). In summary, a pattern was observed that if patients had index hospitalizations, they also had significant number of subsequent hospitalizations in future. However, they did not have as many ED visits.

Figure 4.5 Temporal Use of Healthcare Services after an Inpatient Admission (N=203)



ED= Emergency department, SCD= Sickle cell disease

4.4 Results Summary

Table 4.13 provides a summary of the study objectives, statistical tests and results for the hypotheses.

Table 4.13 Summary of Objectives, Hypotheses, and Statistical Tests

Objective	Hypotheses	Procedure/Statistical Test	Results
1. To describe SCD patient demographics (by SCD index drug type, i.e., HU, opioid analgesics, non-opioid analgesics) and medication and healthcare utilization.	N/A	Descriptive statistics: Means, standard deviation	N/A
	N/A	Frequencies	N/A
2. To determine if there are differences in the type of SCD index therapy (HU, opioid analgesics, non-opioid analgesics, dual index therapy) by age group.	**H_{2A}:** *The proportion of patients using hydroxyurea as index therapy decreases significantly with an increase in age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Failed to Reject
	H_{2B}: *The proportion of patients using opioid analgesics as index therapy increases significantly with an increase in age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Failed to Reject
	Ho_{2C}: *There is no significant difference in proportion of patients using non-opioid analgesics as index therapy among various age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Rejected
	H_{2D}: *The proportion of patients using dual drugs as index therapy increases significantly with an increase in age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Failed to Reject

Table 4.13, continued

Objective	Hypotheses	Procedure/Statistical Test	Results
3. To determine if there are differences in SCD-related prescription drug utilization among patients by age group.	**H_{3A}:** *Adherence to hydroxyurea decreases significantly with an increase in age group.*	ANOVA Duncan's post-hoc analysis	Failed to Reject
	H_{3B}: *The mean total days' supply of opioid analgesics increases significantly with an increase in age groups.*	Kruskal-Wallis test Pairwise comparisons using Dwass, Steel, Critchlow-Fligner (dscf) method	Failed to Reject
	H_{3C}: *The mean total days' supply of non-opioid analgesics increases significantly with an increase in age groups.*	Kruskal-Wallis test Pairwise comparisons using Dwass, Steel, Critchlow-Fligner (DSCF) method	Failed to Reject
4. To determine whether there are differences in SCD-related healthcare utilization (ED visits, inpatient visits, outpatient visits, all-cause prescription drug utilization) among patients by age group.	**H_{4A}:** *The proportion of patients with one or more SCD-related emergency department visits increases significantly with an increase in age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Failed to Reject
	H_{4B}: *The proportion of patients with one or more SCD-related hospital admission increases significantly with an increase in age groups.*	Chi-square test; Pairwise chi-square comparisons with Bonferroni correction	Failed to Reject

Table 4.13, continued

Objective	Hypotheses	Procedure/Statistical Test	Results
	H_{4C}: *The number of SCD-related outpatient visits increases significantly with increase in age groups.*	Kruskal-Wallis test Pairwise comparisons using Dwass, Steel, Critchlow-Fligner (DSCF) method	Failed to Reject
	H_{4D}: *The mean number of all-cause prescription medications increases with increase in age groups.*	ANOVA Duncan's post-hoc analysis	Failed to Reject
5. To describe temporal use of healthcare services after an ED visit or hospitalization.	N/A	Descriptive statistics: Frequencies	N/A

SCD=Sickle Cell Disease; **ED**=Emergency Department; **ANOVA**= Analysis of Variance

CHAPTER FIVE: DISCUSSION

5.1 Chapter Overview

This chapter provides a discussion of the study results. First, a brief review of the study rationale is presented. Second, the study findings are discussed, along with the potential explanations and comparison with the results from other studies. Finally, the limitations of the present study, the conclusions and directions for future research are presented.

5.2 Review of Study Rationale

The purpose of this study was to explore the real-world medication utilization and healthcare service utilization in SCD management among Texas Medicaid patients of different age groups. As guidelines for medication use (HU and opioid analgesics) differ based on age groups of patients with SCD, it seemed pertinent to explore real-world medication utilization, especially for HU and opioid analgesics, by age groups. Additionally, it was essential to understand the temporal healthcare utilization patterns in SCD management among patients of different age groups to identify gaps in care and where interventions may be needed. There are a few studies that have examined HU, opioid analgesic and healthcare service utilization among either pediatric or adult patients with SCD using state Medicaid databases.[68, 74-78] These studies, along with three guidelines [3, 43, 56] on SCD management and several other studies, will be used to compare and explain the findings for each of the study objectives. [12, 13, 30, 31, 41, 50, 56, 64-66, 69-73, 88, 89, 93-96]

5.3 Study Objectives

5.3.1 Objective 1

Objective 1 was to describe SCD patient demographic characteristics, medication utilization and healthcare service utilization characteristics. The majority of patients were female

(62.5%) with mean (±SD) age of 19.1 (±14.6) years. The mean age of patients in the current study was similar to that in the North Carolina Medicaid study which included children and adults with SCD of similar age range (age < 65 years) with mean age of 21 (±12.2) years.[68] Other studies in literature examined SCD medication and/or resource utilization among either children or adults.[74-78, 84, 93, 95, 107] The current study is one of the few studies that have examined both pediatric and adult patients with SCD. Hence, the mean age of patients was not compared with many other studies due to difference in age range of study samples.

Even though SCD affects males and females equally, 62.5 percent of the current study sample was comprised of females, which was almost identical to the studies by Han et al. [107] and Smith et al.[84] (63% females, 37% males) that investigated the patterns of opioid use in patients with SCD and found females were more likely to use analgesics than males. This similarity in gender proportion can be attributed to the way index date is defined in the current study. Index date was defined as the date of dispensing of first SCD-related drug (HU, opioid, non-opioid or dual analgesics) during the follow-up period and most of the patients (93.5%) included in the study had either opioid, non-opioid or dual analgesics as their index drug. On observing the gender distribution within each index drug type, it was evident that while males and females had equal likelihood of receiving HU (female= 50.3%), females were more likely to receive opioids (females=60.7%), non-opioids (females= 61.3%) and combination of opioids and non-opioids (80.5%).

As for the SCD-related index drug therapy use, most of the patients (45.7%) were prescribed opioid analgesics, followed by non-opioid analgesics (36.6%). The prevalent use of opioid and non-opioid analgesics was expected as they are the drugs of choice prescribed to manage the most common complications of SCD (i.e., VOC, leg ulcers) as per the NHLBI[3],

NICE[56] and APS[43] guidelines. Multiple studies, such as Ballas et al.[50] where 100 percent patients in the cohort utilized opioid or non-opioid analgesics to manage SCD pain, also reflect common use of opioid and non-opioid analgesics among patients with SCD, similar to the results seen in the current study.[14, 15, 42, 50, 84, 107, 108] About 11 percent of patients were prescribed dual therapy (i.e., opioid as well as non-opioid analgesics), which was likely to limit the opioid consumption among patients as recommended in guidelines and several studies.[3, 14, 15, 16] On the contrary, only 6.5 percent patients had HU as their index therapy. This was also expected due to the low prevalence and utilization of HU among patients with SCD as observed in several retrospective database studies from different states in the US.[68, 72, 73-78] Moreover, NHLBI guidelines recommend HU use mainly among children and adults with severe SCD.[3]

To understand SCD-related prescription drug utilization, adherence of HU, in terms of MPR, and total days' supply of opioid and non-opioid analgesics were measured. Adherence of HU was suboptimal, with mean MPR of HU as 47.5 (±31.4) percent. Mean HU MPR closely resembled the results of a study by Thornburg et al. where HU adherence was 49 percent based on pharmacy refill data.[72] Suboptimal HU adherence was expected as the trend was also observed in several pharmacy claims studies from other states in the US. [68, 73-78] For opioids and non-opioids, the median annual days' supplies (opioids=10; non-opioids=15) were much lower than the mean annual days' supplies [opioids=47.5 (±103.6); non-opioids=31.9 (±53.8)], which shows that a significant proportion of patients required analgesic therapy for only a few days, perhaps due to one or two pain crisis events. However, a significant proportion of patients, who may have had severe SCD with three or more pain crisis events, might have been prescribed analgesic therapy for longer periods throughout the year, as was also observed in the Han et al.[108] study. Hence, the wide range of total annual days' supply of analgesics could allude to the wide difference in

utilization of analgesics based on SCD severity among the study.[108] Moreover, the wide range could also be due to the inclusion of both pediatric and adult patients in this study.

Regarding healthcare service utilization among patients with SCD, about 70 percent of the study cohort had no SCD-related ED visit and about 78 percent had no SCD-related hospitalization during the 12-month follow up period. This result is consistent with findings from the study by Shankar et al. conducted among children and adults with SCD enrolled in Tennessee Medicaid, where 60-70 percent of patients did not have any hospitalizations and 50-60 percent patients did not have any ED visits.[94] The plausible reason behind these findings could be that many patients with SCD do not require emergency or intensive medical care and have mild SCD symptoms that can be managed at home with over-the-counter analgesics or non-pharmacological interventions such as application of heat or ice packs, massage, therapeutic exercises, acupressure, or distraction.[14, 15, 92] In the study cohort, the mean number of annual ED visits was 1.2 ± 4.5 and mean annual hospitalizations was 1.8 ± 6.9. These results are similar to findings from previous studies such as Brousseau et al.[89] [mean ED visits=1.08 (1.04-1.11), mean hospitalizations=1.52 (1.48-1.55)], Mvundura et al.[93] [mean ED visits=1.36, mean hospitalization=0.91 among children 1-17 years-old], and Shankar et al.[94] [mean ED visits ranging from 0.8 to 3.1, mean hospitalizations ranging from 0.6 to 2.0 among various age groups].

As for outpatient visits and all-cause prescription drug use in the current study, mean annual SCD-related outpatient visits was 4.0 ± 8.4 and mean number of all-cause prescription medications was 14.3 ± 12.0. This was similar to findings of Hemker et al. study where mean SCD-related outpatient visits among Wisconsin Medicaid patients with SCD ranged around 3.3 to 5.8.[90] Mvundura et al. reported around 11-12 mean annual outpatient visits, but they seemingly reported all-cause outpatient visits and not just SCD-related visits.[93] Overall, the healthcare service

utilization varies widely based on several factors, such as SCD severity, age, gender, access to health care facilities and knowledge about disease and its timely management.

5.3.2 Objective 2

Objective 2 was to determine whether type of SCD index therapy differed by age group. Mean age differed significantly by SCD index drug type. On an average, HU (mean age= 14.1±11.9 years) and non-opioid (mean age= 15.5±14.2 years) index users were younger than opioid (mean age= 22.3±15.3 years) and dual therapy (mean age= 20.9±10.7 years) index users. Children aged 2-12 years comprised the majority (57.5%) of HU index users, while older adults aged 41-63 years had the lowest prevalence (4.6%). While observing the pattern of HU index therapy utilization by age group, a declining trend was observed with increasing age group, where about 9 percent children aged 2-12 received HU index therapy as compared to just 3.7 percent of 26-40 and 2.9 percent of patients aged 41-63. The trend is understandable when NHLBI guidelines and existing literature are taken into account. While evidence-based NHLBI guidelines strongly recommend HU use among all children and young adolescents with SCD to prevent complications, they only recommend HU use among adults with severe SCD.[3, 13, 64-66] Despite guideline recommendations, HU utilization was low among all age groups, comprising only 6.5 percent (153 out of 2,339) of all index drug therapies. This was consistent with findings from existing literature that concluded low HU utilization among patients with SCD. [12, 67, 68, 74-78]

As previously discussed, opioid and non-opioid analgesics are drugs of choice to manage most common SCD complications. Overall, in the study cohort, opioid index therapy comprised the largest index drug category with nearly 46 percent (1,069 out of 2,339) of all index drug prescriptions. Specifically, for opioid index drug utilization by age group, an upward trend was observed with increasing age group. While opioid index use was only about 35 to 40 percent in

children and adolescents, opioid index use increased significantly among adults, with about 65 percent of older adults receiving an opioid analgesic as index drug. This finding was expected because all SCD guidelines recommend prompt and aggressive treatment with parenteral opioids to manage acute VOC pain[3, 43, 56] and NHLBI recommends oral opioids to manage severe chronic SCD-related pain.[3] At the same time, NHLBI guidelines recommend usage of non-opioids for mild and moderate pain, especially in children, to limit their opioid intake. The overall findings regarding substantial opioid use align with the studies in literature that point towards prevalent use of opioids to manage SCD-related pain. [14, 50, 84, 107, 108]

As stated above, non-opioid analgesics are recommended to manage mild to moderate SCD-related pain.[3, 56] They are also prescribed to avoid excessive opioid analgesic intake which could lead to opioid habituation and tolerance. [14,16,50] While observing non-opioid index drug utilization by age group, it is evident that non-opioid index use is significantly more common among children (48.2%) and adolescents (41.2%) as compared to adults (~22-28%), which may be to limit their opioid intake.

Under dual therapy, non-opioids are prescribed as an adjuvant therapy along with opioids to limit opioid intake and control pain. While observing dual index therapy utilization by age group, young adults of age groups 18-25 (23.7%) and 26-40 (15.7%) had significantly higher proportion of dual index therapy as compared to children (6.1%), adolescents (10.7%) and older adults (3.7%). Interestingly, a well-known study by Platt et al., revealed that rate of pain episodes requiring a clinic visit was significantly higher among patients with SCD aged 20 to 29 years old as compared to patients 0 to 9, 40 to 49, and ≥50 years old.[8] A similar trend was also observed in another study by Brousseau et al.[89] This could explain the higher use of dual analgesic therapy to control pain and limit overall opioid consumption during frequent medical visits among patients

of age groups 18-25 and 26-40 with severe SCD. Also notable is that, while not statistically significant, dual therapy use was higher (23.7% vs. 15.7%) in 18-25 age group as compared to 26-40, which also includes patients aged 30-40 who might not have as frequent pain episodes.[8]

5.3.3 Objective 3

Objective 3 was to determine if there were differences in mean HU medication adherence and annual total days' supply of opioid and non-opioid analgesics by age group.

While drug effectiveness trials reported very high HU adherence ranging between 74 and 94 percent, the results of current study were compared to previous studies that utilized pharmacy claims to measure HU adherence. In the current study, mean HU adherence ranged from 34.7% (±31.1%) to 65.2% (±28.3%) in index HU users and from 29.5% (±23.1%) to 58.9% (±30.7%) in all HU users. HU adherence was highest in age group 2-12 years (index HU MPR=65.2% ± 28.3%; all HU MPR=58.9% ± 30.7%), which was very similar to the mean HU MPR observed in study by Anders et al. (mean MPR=67.8%) among children with SCD aged 0-9 years enrolled in New York State Medicaid[75] and an MPR of 60.5% observed in study by Patel et al. among children aged 0-20 years enrolled in Missouri Medicaid.[77] The relatively high HU adherence among children and adolescents was expected as NHLBI guidelines strongly recommend HU use among all children and young adolescents with SCD to prevent SCD complications.[3]

Despite the different methods used to report HU adherence (mean MPR vs. proportion of patients with MPR ≥80%), all previous studies concluded low HU adherence, especially among adults with SCD. [68, 74] In the current study, HU adherence was lower (mean MPR=~30%-35%) among young, middle-aged and older adults as compared to children, for HU index use as well as all HU use, with an exception of HU index users of 41-63 years age group. This trend of low HU

use is consistent with findings from studies conducted among patients enrolled in Florida Medicaid[74] (MPR<60% in 70% study population) and North Carolina Medicaid[68] (mean MPR=60%, MPR<80% in 65% study population). The North Carolina study reported mean MPR of 60 percent across the whole study population aged <65 years and hence, cannot be directly compared to mean MPR of about 30 percent among adults in the current study.[68] A Florida Medicaid study reported discontinuation of HU in at least 30 percent patients and mean MPR of less than 60 percent in about 70 percent of the study cohort.[74] Overall, these findings are consistent with the current study. To some extent, the low HU adherence among adults could be explained by NHLBI guidelines, which only recommend HU use in adults experiencing three or more VOCs in a 12-month period, or having a history of severe acute chest syndrome, chronic anemia or severe SCD-related pain.[3] In this study, the very small proportion of adult patients aged 41-63 who had HU as index drug may have had a history of severe SCD, which could explain a relatively higher HU MPR (52.6% ± 32.3%).

Opioid utilization among patients with SCD was examined using mean annual total days' supply of opioid analgesics. As per the trends observed in this study for opioid index use and overall opioid use, opioid days' supply was lowest among children (13.0 ± 15.0) and adolescents (17.2 ± 32.5), increased significantly among young (56.2 ± 111.3) and middle-aged adults (86.0 ± 138.3) and was highest among older adults (158.8 ± 180.8). The profound difference in opioid use among patients of different age groups can possibly be explained due to reasons such as prevalence and nature of pain, HU use, guideline recommendations, dosing differences by age groups and prescriber perceptions. Previous studies have reported lower prevalence of SCD-related pain among children and adolescents (pain on 8.4% days surveyed)[46] as compared to adults (pain on 55% days surveyed)[9] with SCD. While children and adolescents mostly experience acute, episodic

nociceptive pain, adults with SCD experience more severe and chronic pain that requires on-going/long-term opioid analgesic use.[91, 107, 108] Studies have also shown how opioids are used extensively (opioid use on ~35-40% days in general, in 60% follow-up visits, 100% of inpatient and outpatient visits) to manage acute and chronic pain among adults with SCD.[50, 84, 107, 108] Moreover, clinical trials and observational studies provide evidence of effectiveness of HU among patients with SCD.[13,62-66,69,70,71] As stated earlier, NHLBI guidelines strongly recommend HU use among children and adolescents to prevent SCD complications, but only recommend HU among adults with severe SCD with recurrent complications.[3] The significant difference in HU utilization and adherence among patients of different age groups might also contribute to differences in prevalence of SCD complications and subsequent opioid use. Finally, Fearon et al. reported pediatricians' hesitation in prescribing opioids among children due to fear of potential opioid tolerance and dependence.[81] This could also explain low use of opioids among children with SCD.

As expected, non-opioid analgesic index use and overall use followed similar trend as opioid analgesic use. Non-opioid analgesic days' supply was lowest among children (14.8 ± 17.0), increased significantly among adolescents (33.2 ± 41.0), young (26.1 ± 39.3) and middle-aged adults (41.5 ± 57.5) and was highest among older adults (133.6 ± 138.4). As per SCD guidelines and previous studies, non-opioid analgesics are prescribed for managing mild to moderate SCD-related pain and prescribed as adjunct therapy to limit opioid intake and provide further relief to patients in case of severe pain.[3, 43, 50, 56] The higher total days' supply of non-opioid analgesics among adults as compared to children could possibly be attributed to previously stated reasons such as higher prevalence of chronic pain and other SCD-related complications, such as leg ulcers, and lower HU initiation and adherence rates among adults with SCD. [50, 91, 107, 108]

5.3.4 Objective 4

Objective 4 was to determine if there were differences in SCD-related healthcare service utilization (ED, inpatient, and outpatient visits, all-cause prescription drugs) by age group.

Utilization of SCD-related ED visits was measured as proportion of patients with one or more ED visits with SCD diagnosis within the 12-month follow up period among different age groups. In the current study, adolescents (21.3%) and older adults (24.2%) had lower proportion, while children (33.2%), young adults (29.3%) and middle-aged adults (32.3%) had higher proportion of patients with SCD-related ED visits. Similarly, utilization of SCD-related hospitalizations was measured as proportion of patients with one or more hospitalizations with SCD diagnosis among different age groups. Adolescents (12.9%) and older adults (18.0%) had the lower proportion, while children (23.0%), young adults (25.1%) and middle-aged adults (22.4%) had higher proportion of patients with SCD-related hospitalizations. Higher ED visits and hospitalizations among patients of age groups 18-25 and 26-40 were consistent with existing literature. Studies suggest that most (~about 97% in Woods et al. study)[95] SCD-related ED visits and hospitalizations have VOC pain crisis as the primary diagnosis. Multiple studies have also shown that patients with SCD of ages 18-30 years have higher VOC crisis events, SCD-related mortality, ED visits and hospitalizations as compared to children and older adults, possibly due to reasons such as lack of access to healthcare facilities, lack of knowledge about their disease and need for preventive interventions resulting in sudden and severe complications.[8, 89, 90, 92, 94] Furthermore, while not statistically significant, HU adherence was lowest among age groups 18-25 and 26-40 in the current study. Hence, it is possible that the patients of age groups 18-25 and 26-40 have more frequent pain crises requiring medical care through ED visits and hospitalizations. Interestingly, the current study also showed higher than expected proportion of

children of age group 2-12 with one or more ED visits and hospitalizations. This could be due to underutilization and low adherence of HU, but further research needs to be done to identify reasons behind this finding.

Utilization of SCD-related outpatient visits was measured as mean number of outpatient visits with SCD diagnosis within the 12-month follow up period among different age groups. In the current study, adolescents (2.9 ± 5.4) and young adults (3.6 ± 8.4) seemed to have lower mean number of outpatient visits, while children (4.5 ± 7.6) and adults of age groups 26-40 (4.3 ± 10.6) and 41-63 (3.9 ± 8.9) had, not statistically significantly, but still higher mean outpatient visits. This finding was also seen in Hemker et al. study which concluded that patients transitioning from childhood to adulthood and young adults have fewer outpatient visits and greater reliance on ED visits as compared to children and older adults aged 31-45 years. Hence, fewer outpatient visits among adolescents and young adults in the current study could be because these patients are transitioning from pediatric to adult providers.[90]

`As for all-cause prescription drug use, mean number of unique all-cause prescription medications were compared among different age groups. Adolescents (11.8 ± 9.8) and young adults (11.9 ± 10.8) had the lowest number of prescription drugs, children (13.7 ± 9.9) and middle-aged adults (14.8 ± 13.2) had higher, and finally, the older adults (22.4 ± 16.3) had the highest number of unique prescription medications. Lower use of prescription medications among adolescents and young adults could be due to the lack of access to providers during the transition phase from childhood to adulthood as seen in the study by Hemker et al.[90] Higher number of prescription medications among children of age group 2-12 years can be explained by evidence and recommendations from NHLBI guidelines. Children, especially the ones aged five years and below, are highly prone to bacterial infections, and hence, NHLBI guidelines strongly recommend

prophylactic antibiotic use among children.[1, 3] Finally, the trend of high medication use among older adults may be due to an increase in prevalence of chronic conditions, which are often further exacerbated due to SCD.[3] Hence, older adults may use multiple medications to manage their chronic conditions.

5.3.5 Objective 5

Objective 5 was a descriptive objective to understand the temporal patterns of use of healthcare services in SCD. About 75 percent patients had an ED visit as their index service type and about 25 percent had a hospitalization. This seems to suggest that a large proportion of patients might experience an acute VOC event that requires urgent care, similar to findings of Woods et al. study.[95] The results also indicate that most patients (~85%) had a subsequent outpatient visit which could have been a referral to a primary care physician (PCP) or a hematologist, after being discharged from the ED. Moreover, the outpatient visit to a PCP or hematologist may have been required since a blood test is needed prior to initiating HU therapy. The 15 percent that were admitted to the hospital after the ED visit may have had a severe crisis needing further observation. For the third and fourth service in the index ED visit group, about 18 percent of patients had another ED visit, which may indicate that these were more severe patients who suffer frequent VOC events requiring urgent medical care. This result may be explained by findings reported by Platt et al., in which they reported that a small proportion of patients with SCD have three to ten VOC events in a year and frequently require medical care.[8]

Interestingly, the 25 percent of patients who had a hospitalization as an index service type, had hospitalizations even in the subsequent services (second service- 42.8%, third service- 53.2% and fourth service- 38.4% hospitalizations). However, a smaller proportion of these patients had ED visits. Overall among the study population of objective 5, outpatient visits were a common

service availed consistently by about 30 to 40 percent of patients. However, SCD-related prescription drug use as subsequent services was observed in a smaller proportion of patients (~20% or less).

5.4 Study Limitations

Although this study is important in establishing the medication and healthcare utilization patterns among patients with SCD, there are some important limitations. First, the scope of the study is limited by the information collected in the Texas Medicaid database. The database may not include over-the-counter (OTC) analgesics or any other analgesics not covered under Texas Medicaid formulary. However, several of the most common OTC analgesics are covered on the formulary (see Table 3.1, non-opioid analgesics). Moreover, the database does not capture any prescription or OTC medication that is prescribed by providers but not paid for or claimed through Texas Medicaid, i.e., bought using out-of-pocket payment. Second, the first SCD diagnosis within the observation period may not represent the first-ever SCD diagnosis for the patient since this disease is typically identified at birth. The pre-index period has been defined as six months before index date where no SCD-related drug (HU, opioid and non-opioid analgesics) was used. Third, opioid and non-opioid analgesics could have been used for reasons other than SCD complications, such as a broken arm, headache, or other injury. Thus, this could have led to an overestimate regarding SCD-related analgesic use. Fourth, "adherence" or "total days' supply" from secondary claims databases not necessarily represent the actual days patients take their medication. Finally, external validity of study findings may be limited and may not be generalizable to other SCD patient populations outside of Texas Medicaid.

5.5 Conclusions and Future Directions

In summary, all patients with SCD enrolled in Texas Medicaid have low utilization and adherence to HU and interventions to increase HU adoption and its adherence could benefit patients by better managing their SCD complications. Opioid use is prevalent among all patients with SCD, and there is an upward trend in the opioid use with increasing age group. Patients with SCD also have high use of healthcare services such as emergency department, inpatient and outpatient visits, especially among adolescents and young adults who are transitioning from childhood to adulthood.

The following topics may be areas of future research among patients with SCD:

1. This study identified major underuse of HU, with mean HU adherence ranging around 35 to 65 percent. Discussed below are some of the barriers to HU uptake and adherence. Firstly, to avoid the risk of HU toxicity, cytopenia and bone-marrow suppression, patients are required to undergo blood tests prior to initiation or refilling HU prescriptions. Secondly, because of issues regarding access to a hematologist[109], patients with SCD are often managed by PCPs who may not be adequately trained in this area. Thirdly, about two-thirds of this study cohort were female and in the 18-25 and 26-40 year age group, which are during child-bearing years. Due to its teratogenic nature, HU cannot be used among women who are planning to get pregnant, are pregnant, or are breast-feeding. Because of the abovementioned factors related to low HU use, researchers should conduct in-depth qualitative research to identify issues associated with HU underuse and then consider interventions to improve HU uptake and adherence. Adolescents and young adults should be populations of focus because they had higher utilization of ED visits and hospitalizations.

2. Because children aged 2-12 years had higher HU use and adherence, we expected that ED visits and hospitalizations would be lower than other age groups. However, the results did not support this hypothesis. Thus, further explanation is needed regarding incongruent use of HU and emergent healthcare services in this age group.
3. Patients of age groups 18-25 and 26-40 years were found to have higher ED visits and hospitalizations. As previously stated, individuals 18-25 may be transitioning from pediatric to adult services and there may be gaps in this transition of care. Thus, further research is needed to identify characteristics of high utilizers and design strategies and interventions specific to this age group to promote more efficient care transitions.
4. Previous studies have identified health-related and societal stigma associated with SCD. As SCD is most prevalent among African American population, these patients also experience opioid-based stigmas. SCD stigma not only impacts the physiological and psychological well-being of patients, but also acts as barrier against effective patient-provider relationships and care-seeking behaviors among adolescents and adults with SCD. Thus, qualitative studies should be conducted among adolescents and young adults to identify issues associated with high ED and inpatient service utilization and low outpatient use. Consequently, specific interventions should be designed to create awareness, reduce stigma, and help these patients overcome barriers to optimal medical care for SCD.
5. Finally, it will be interesting to evaluate the impact of novel SCD therapies entering the market, such as Endari® and gene therapy, on the trends of prescription drug and healthcare service utilization among patients with SCD.

Appendix

Appendix A1. ICD-9 and ICD-10 Codes for Sickle Cell Disease

ICD-9-CM	ICD-10-CM	Description
282.60	D57	Sickle-cell anemia or Sickle-cell disease
282.61	D57.00	Sickle-cell with Hb-S
282.62	D57.00	Sickle-cell with crisis
---	D57.1	Sickle-cell without crisis
282.63	D57.20	Sickle-cell with Hb-C without crisis
282.64	D57.21	Sickle-cell with Hb-C with crisis[a]
282.68	D57.80	Sickle-cell with other abnormal hemoglobin[b] without crisis
282.69	D57.819	Sickle-cell with other abnormal hemoglobin with crisis[a]
282.41	D57.40	Sickle-cell with thalassemia without crisis
282.42	D57.41	Sickle-cell with thalassemia with crisis
282.5	D57.3	Sickle-cell trait

ICD- International Classification of Diseases

[a]Vaso-occlusive crisis (VOC) event

[b]Other abnormal hemoglobin: Hb-D, Hb-E, Hb-G, Hb-J, Hb-K, Hb-O, Hb-P

Appendix A2. ICD-9 Codes for Complications Associated with Sickle Cell Disease

ICD-9-CM	Description
517.3	Acute Chest Syndrome
995.92 (from Severe Sepsis)	Acute Multiorgan Failure
429.3	Cardiomegaly
425.xx	Cardiomyopathy
574.xx, 575.xx	Gall Stones, Cholelithiasis
427.xx	Dysrhythmia
 376.01 362.3x	Eye Disorders Orbital Cellulitis Retinal Vascular Occlusion
 682.x, 681.x 047.x, 320.x, 321.x 730.xx 733.xx	Infection Cellulitis Meningitis Osteomyelitis Osteonecrosis
707.1x	Leg Ulcers
607.3	Priapism
416.0	Pulmonary Hypertension
584.6, 584.7	Renal Failure, Acute
403.xx-404.xx	Renal Failure, Chronic
430.xx-434.xx	Stroke, Ischemic

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Vita

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