# Opioid Use in Adults With Sickle Cell Disease Hospitalized During Vaso-Occlusive Crisis: A Systematic Review

Jennel C. Osborne[a, d], Zainab Osakwe[b], Michelle Odlum[c]

## Abstract

**Background:** While pain is the hallmark of sickle cell disease (SCD), healthcare personnel are often ill-equipped to adequately treat patients who present in vaso-occlusive crisis (VOC). Although symptom severity varies from individual to individual, SCD is characterized by intervallic pain as a result of oxygen deprivation in tissues and organs. Regardless of pain severity, SCD patients are often viewed as drug seekers by healthcare personnel who have concerns regarding patients' dependence on opioids which may lead to addiction. The objective was to assess the types and amount of opioids used to treat VOC in comparison to Centers for Disease Control opioid prescription guidelines.

**Methods:** Literature search was conducted using CINAHL, PubMed, the Cochrane Library, Web of Science and hand search. Data were analyzed from 1999 to 2018. Randomized trials, observational, and case studies involved hospitalized adults with SCD who were prescribed opioids to treat VOC. Quality assessment was conducted using Downs and Black checklist. Meta-analysis was not conducted.

**Results:** Five studies were conducted in the USA, Arabia and the Netherlands, and the USA and Canada were included. Participants were treated with either morphine or morphine milligram equivalent (MME). No study used the same method of opioid administration.

**Conclusions:** Patients with SCD who are hospitalized secondary to VOC mostly received opioids for pain well within the Centers for Disease Control and Prevention prescription guidelines. No uniform method exists. Additional research is warranted.

**Keywords:** Opioid; Sickle cell disease; Vaso-occlusive crisis; Systematic review

[a]Long Island University Harriet Rothkopf Heilbrunn School of Nursing, Brooklyn, NY, USA
[b]Adelphi University College of Nursing and Public Health, Garden City, NY, USA
[c]Columbia University Irving Medical Center, New York, NY, USA
[d]Corresponding Author: Jennel Osborne, Long Island University Harriet Rothkopf Heilbrunn School of Nursing, NY 11201-5372, USA. Email: Jennel.Osborne@liu.edu

## Introduction

Sickle cell disease (SCD) is a genetic disorder that occurs as a result of a β-globin gene variation known as hemoglobin S (Hb S) or sickle hemoglobin [1]. SCD affects millions of people worldwide and approximately 100,000 Americans of African, Spanish, Saudi Arabian, Indian and Mediterranean descent [2]. Americans of African descent (non-Hispanic black) experience the highest prevalence of SCD followed by Americans of Hispanic/Latino descent [3, 4], with other ethnic groups experiencing SCD prevalence to a lesser extent.

Individuals with SCD are at risk for acute complications like anemia, stroke, acute chest syndrome and periodic painful vaso-occlusive crisis (VOC) [5]. Periodic painful VOC occurs when vessels become occluded or tissue becomes damaged as a result of oxygen deprivation; this is the hallmark clinical manifestation of SCD [6]. Tissue damage as a result of painful VOC may occur in the brain, spleen, lungs, eyes and other tissues like bone [7]. VOC often leads to opioid treatment and/or frequent hospitalization, and is the most common cause of morbidity in this population [6, 8]. Morbidity has been the highest in patients who report the highest pain rates compared to those with lower pain rates [9]. Painful VOC causes significant illness and profoundly impacts health-related quality of life in patients with SCD [10]. In a 2018 study of quality of life in a group of children with SCD, perception was the lowest among Latino and non-Latino children with SCD who were hospitalized more frequently in the prior year, compared to their counterparts with SCD with little or no hospitalization in the prior year [11].

Persons with SCD are increasingly living longer. In previous decades, life expectancy for SCD was on average 14

### Key Points

- Question: What pain management therapies are prescribed for sickle cell disease patients during vaso-occlusive crisis?
- Findings: In this systematic review, the number of randomized clinical trials included is small and the differences in treatment regimen were minimal.
- Meaning: The current literature does not demonstrate the clinical advantage of using a variety of treatment regimens that do not include opioid therapy for sickle cell disease patients during vaso-occlusive crisis.

years [12]. Since then, identification via neonatal screening has considerably decreased childhood mortality [13]. Neonatal screening of cord blood for SCD was first reported in 1972 in the UK by researchers interested in neonatal hemoglobin screening [14], and has since been implemented throughout the USA as part of a uniform panel of diseases as part of newborn screening. With the advent of preventative measures such as prophylactic management and screening started in infancy, the median age at death in 2005 was cited as 38 years for males and 42 years for females [15]. For prophylactic management, twice daily penicillin is recommended to start in early infancy after newborn screening and continue throughout age 5 and older. Vaccination against pneumococcal and other encapsulated pathogens and routine health management with a healthcare provider who has expertise in SCD are also recommended for prophylactic management [16].

## Treatment

SCD pain may range from mild to severe [6, 17]. Typically, mild pain is treated at home with oral analgesics [18], while severe pain during VOC is treated in the emergency room or during hospitalization with opioids [18, 19], non-steroidal anti-inflammatory drugs and intravenous hydration in addition to other pain-relieving therapies [20].

Because uncontrolled pain is the hallmark of SCD, healthcare providers must be prepared to treat patients with SCD with effective pain management similar to other patients with chronic. Yet, most healthcare providers are often not equipped with adequate information on how to treat patients who frequently present to emergency departments or ambulatory care settings with painful VOC [21, 22]. Substantial show that healthcare providers often view SCD patients in VOC as drug seekers because of the stigma associated with needing and seeking opioids for SCD treatment [23-25]. Furthermore, there is evidence of racial bias within the healthcare system that poses substantial barriers for patients with SCD [23].

With the current opioid crisis, dispensers of opioid prescriptions are more aware of the potential for, and actual opioid abuse among patients diagnosed with various diseases [26-28]. This awareness results in a hesitancy of prescribers and the treatment team to recommend and/or administer opioids to patients with SCD [29]. This awareness of opioid abuse by providers appears to be an added disadvantage to patients with SCD experiencing VOC because opioids are one of the main treatment methods that exist to effectively treat VOC.

Focusing on opioid use in hospitalized adult patients with SCD, the objectives of this paper were to address the following questions: 1) Which opioids are used to treat VOC in hospitalized patients with SCD; and 2) What dose of opioids resulted in decreased sickle cell pain in hospitalized patients. Specific to these objectives, this review includes a presentation of the current evidence that pertains to pain rating on admission, the method and amount of opioids administered, and pain response during VOC in hospitalized sickle cell patients.

## Materials and Methods

### Search strategy

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [30] was used to guide this systematic review. We performed a comprehensive computerized literature search in addition to hand searches restricted to English language and studies with humans using search terms "Opioids" AND "Sickle cell" AND "Hospital". All searches were conducted for articles published between January 1999 and March 2018. This strategy yielded 231 citations in CINAHL (22 hits), PubMed (137 hits), Cochrane Library (17 hits), Web of Science (53 hits) and hand search (two hits). The deletion of duplicate articles (n = 69) left 162 articles for screening.

### *Inclusion criteria*

Articles were included if they: 1) were written in English; 2) were quantitative studies that evaluated opioid use in hospitalized patients with SCD; 3) were published between January 1999 and March 2018; 4) included participants aged 18 years or older; and 5) were conducted using named opioid/s with dosages, as treatment.

### *Exclusion criteria*

Articles were excluded if they: 1) included children (n = 58); 2) were not of quantitative design (n = 24); 3) were not conducted during hospitalization (n = 22); 4) were review articles (n = 18); 5) were non-opioid focused (n = 15); and 6) were not SCD diagnosis (n = 5). Also excluded were studies that closed early (n = 1), studies that measured pain during C-section (n = 1) and studies conducted during pregnancy (n = 1).

### Data extraction

Titles and abstracts were reviewed for applicability and retained as appropriate by a single reviewer, while co-investigator verified data accuracy. Discrepancies were resolved through discussion. Full-text articles were screened using inclusion/exclusion criteria, leaving five articles for inclusion in this review. Information regarding author, study sample, location of study, age in years, gender and type of SCD were culled from the articles. Information regarding study design, pain rating on admission, opioid and dosage, observation period and pain response, and major findings were selected from the articles.

### Quality assessment and analysis

Studies were assessed for quality using Downs and Black checklist [31] for the assessment of the methodological qual-

**Table 1.** Demographic Data of Sample

| Author | Location | Study sample size | Age in years | Gender | Type of SCD |
|---|---|---|---|---|---|
| Al-Anazi et al, 2017 [33] | Saudi Arabia | 99 | Mean 26.9 | Males 47%, females 52% | Not specified |
| Ballas et al, 2010 [34] | USA and Canada | 299 | 18 - 59 | Male 49%, female 51% | SC $\alpha^+$ thalassemia, n = 298 |
| Desai et al, 2013 [35] | USA | 13 | 22 - 50 | Male 31%, female 69% | HbSS, n = 6; HbS$\beta^0$, n = 2; HbSC, n = 1 |
| Lagas et al, 2010 [36] | the Netherlands | 1 | 61 | Male 100% | HbSC, n = 1 |
| van Beers et al, 2007 [37] | the Netherlands | 19 | 20 - 42 | Male < 50%, female > 50% | HbSS, majority of sample |

SCD: sickle cell disease; SC: sickle cell; HbSS: most severe form of SCD; HbSC: second most common form of SCD; HbS$\beta^0$: severe form of SCD.

ity of randomized and non-randomized studies. The original Downs and Black checklist scored item 27 (refers to study power) as 0 to 5. In another study, the present version of the checklist, item 27 was modified to reflect whether the study or not performed power calculation [32]. The maximum score for item 27 was therefore 1 instead of 5 and thus the highest possible score for the checklist was 28 instead of 32. Score ranges were given corresponding quality levels as previously reported [32] as follows: excellent (26 - 28); good (20 - 25); fair (15 - 19); and poor (< 14). Meta-analysis was not conducted because of the small number of studies included in our review, inconsistency in study designs and interventions.

## Results

### Description of studies

The electronic database and hand search yielded 231 possible studies, 69 of which were duplicates. Based on title and abstract review, 145 studies were excluded, and 17 studies were retrieved for further review. After an initial review of the 17 studies, five met the inclusion criteria and were thus included in this review.

Studies that met inclusion criteria varied broadly in focus and methods of opioid administration. Al-Anazi et al (2017) [33] compared participants' pain intensity and pain relief using patient-controlled analgesia (PCA), or intermittent intravenous (IV) opioid therapy in conjunction with investigating cardiovascular and respiratory adverse events during VOC in patients with SCD [33]. Ballas et al (2010) [34] examined hospital length of stay (LOS) of adult participants with SCD who were enrolled in their multicenter study of hydroxyurea, summarized LOS, parenteral and oral opioid use between hydroxyurea treatment and placebo groups, and between hydroxyurea treatment responders and non-responders, and summarized the type and amount of analgesics used prior to hospitalization. Desai et al (2013) [35] evaluated the safety and efficacy of eptifibatide, an antiplatelet drug, in participants during VOC, using a treatment group in comparison with a placebo group. Desai and colleagues also measured the duration of acute pain episodes, pain intensity, total opioid consumption and acute chest syndrome [35]. Lagas et al (2010) [36] presented a case report of a patient with lethal morphine intoxication; morphine

was administered subcutaneously and intravenously. In their sample of patients with SCD, van Beers et al (2007) [37] compared the efficacy of PCA IV morphine administration with continuous infusion (CI) in participants during VOC. Considering the variety of study aims and methods of opioid administration, a quantitative meta-analysis was not possible. Instead, descriptive analysis and synthesis of findings are presented.

### Demographics

Table 1 describes demographic data including author, study location, sample size, age, gender and SCD type. Two studies each were conducted in the Netherlands [36, 37], one was conducted in the USA and Canada [34], one study was conducted in the USA [35], and one was conducted in Saudi Arabia [33]. Sample sizes ranged from 1 to 299. Most participants were female and ranged in age from 18 to 51 years.

### Pain rating

Researchers varied on how pain was measured. Three studies [33, 36, 37] reported pain rating on admission while two studies [34, 35] did not. Using a pain scale evaluated by using a numerical scale from 0 (mild pain) to 10 (severe pain) where pain intensity between 1 and 2 is mild pain, pain intensity between 3 and 6 is moderate pain, and pain intensity between 7 and 10 is severe pain. A mean pain level of 5.43 ± 1.73 on admission was reported for all participants in one study [33]. Another study [36] reported pain rating on admission as "severe". van Beers et al (2007) [37] reported pain score and interquartile range (IQR) of 72 (63 - 84) for the PCA group and 59 (51 - 85) for the CI group, using a 0 (no pain) to 100 (worst pain) pain scale.

### Primary focus: opioid use during hospitalization

As shown in Supplementary Material 1 (www.thejh.org), participants in all studies were treated with morphine or morphine milligram equivalent (MME) using PCA, intermittent IV opioid administration, or oral administration during hospitalization. Considering that these studies measured opioid use during

hospitalization for the management of pain during VOC, results will be described in more depth since this is one of the main goals of this systematic review. Findings from studies were inconclusive regarding which method of morphine administration provided a significant reduction in pain during VOC.

None of the studies used the same method of opioid administration. Studies varied in their measurement of pain resolution. Al-Anazi et al (2017) [33], for example, compared PCA versus intermittent IV opioid administration groups. For participants in the PCA group, the mean total amount of morphine equivalent dispensed in 72 h was significantly higher (777 ± 175 mg) compared to those in the intermittent IV opioid administration group (149 ± 74 mg) (P < 0.000003); however, participants in the intermittent IV opioid administration group reported a significant reduction (P < 0.0004) in pain level compared to participants in the PCA group [33]. Doses received by the PCA group exceeded the Centers for Disease and Control and Prevention (CDC) prescription guidelines of ≥ 90 MME/day while doses received by the intermittent IV opioid administration group were within CDC guidelines for opioid prescription.

Ballas et al (2010) [34], among other outcomes, reported based on comparison of opioid administration via parenteral versus oral routes. Ballas and colleagues reported no significant difference between groups regarding time to crisis resolution, pain intensity, or time to discharge. The mean (standard error (SE)) daily dose of intravenous MME was calculated for hydroxyurea treatment group (hydroxyurea and placebo) and responders to hydroxyurea group (responders and non-responders). Daily parenteral dose ranged between 41.3 (1.1) in the treatment/placebo group and 54.8 (1.4) in the hydroxyurea response group/responders. The mean (SE) daily oral dose of MME ranged between 32.6 (1.1) in hydroxyurea response group/non-responders and 50.5 (1.4) in hydroxyurea response group/responders. Doses received by both groups were well within the CDC prescription guidelines for opioids prescribed.

Desai et al (2010) [35] reported no significant differences between eptifibatide and placebo groups regarding time to sickle cell crisis resolution, pain intensity, or time to discharge. Desai and colleagues reported a median total dose of 400.2 morphine equivalents for participants in the eptifibatide group and 1,471 morphine equivalents. Desai and colleagues reported that morphine equivalents were usually administered via PCA; they, however, did not report mean daily dose of morphine equivalents which could be compared to the CDC prescription guidelines regarding opioid use of ≥ 90 MME/day.

Lagas et al (2010) [36] reported administering an approximate cumulative daily dose of morphine of 100 mg subcutaneously from day 1 to 5; 10 mg subcutaneously and 29 mg intravenously on day 6 in their case study of a 61-year-old patient in VOC who subsequently died. Doses received by the patient in Lagas and colleagues' case study exceeded the CDC prescription guidelines of ≥ 90 MME/day on days 1 - 5, while doses received on day 6 were within CDC guidelines for opioid prescription.

Van Beers et al (2007) [37] compared PCA versus CI during VOC where they reported a median daily consumption of morphine of 0.5 (0.3 - 0.6) mg/h in the PCA group and 2.4 (1.4 - 4.2) mg/h in the CI group (P < 0.018). Morphine doses received by both groups were well within the CDC prescrip-

tion guidelines for opioid prescription.

## Discussion

Notwithstanding extensive exploration of research examining opioids used for pain relief in adults hospitalized secondary to VOC, we found only five studies that were specifically designed to examine opioid use in hospitalized adult patients with SCD. Given the limited number of articles, a meta-analysis was not appropriate. Based on our review, morphine is used extensively to relieve VOC pain in hospitalized adults. However, results were inconclusive regarding the daily amount of morphine used to treat VOC pain, the reporting of pain rating on admission, and the instrument used to measure pain.

There is a paucity of studies on stand-alone morphine use in pain management of chronic disorders other than SCD during hospitalization. Studies conducted regarding opioid use in pain treatment have revealed various results concerning measurement and reporting of opioid use in hospitalized patients including delays and barriers in the administration of these analgesics [38]. In this review, morphine use among SCD patients hospitalized in VOC varied based on the measurement used by researchers. While other studies did not measure and report morphine use the same as studies included in this review, reasonable comparisons and inferences of morphine use can still be made. In this review, cumulative daily morphine use as reported by Al-Anazi et al (2017) [33] at 48 h post-hospitalization for VOC was 331 ± 101 mg (PCA group) and 45 ± 28 mg (intermittent IV opioid administration group). Al-Anazi et al (2017) [33] reporting for their intermittent IV opioid administration group compared favorably to the total PCA morphine consumption for the placebo group of 99.7 ± 54.7 mg reported by Zengin et al (2015) [39] in their prospective, randomized, placebo-controlled and double-blinded study of adult patients and their consumption of morphine in the first 48 h after laparotomy.

CDC prescription guidelines based on overdose risk when opioids are prescribed for pain, recommend: 1) using caution when prescribing opioids at any dosage; 2) that patients with an increase of opioids ≥ 50 MME daily should be monitored and assessed more frequently; 3) a reduction or discontinuation of opioid therapy if the benefits do not outweigh the harm; and 4) doses ≥ 90 MME/day should be avoided or carefully planned [40]. The distinctive challenges in managing the complications of VOC resulted in CDC recommendations to refer to SCD specific guidelines for pain management. However, misapplication of CDC guidelines was observed, resulting in the CDC's emphasis of treating the pain of SCD beyond the scope of their recommendations [38]. Considering the CDC's recommended guidelines, SCD specific guidelines [38] and the dosages reported by researchers in studies that are included in this review, there appears to remain a gap in practice regarding what is recommended and ultimately prescribed dosing in adults hospitalized in VOC. In their reporting of opioid abuse when treating chronic pain, researchers reported that one of the risk factors associated with morphine addiction and/or overdose in any person, regardless of diagnosis, was the use of >

100 MME/day [41].

With the current focus on the opioid epidemic and considering the non-standardized administration of opioids to relieve VOC, opioid alternatives need to be considered as pain relief measures in conjunction with reduced opioid use. From the SCD patient perspective, differences in opioid prescribing practices since the highlight of the epidemic are observed. Prescribing is seen as more restrictive; prescriptions are heavily monitored and harder to fill. As a result, stigma is heightened, and pain is not well managed as providers focus on the reduced use of pain medication. Consequently, SCD patients are interested in alternative therapies to support effective pain management [42]. Non-addictive alternatives can potentially relieve the stigma associated with opioid use in the SCD population. Researchers evaluated two such non-addictive alternatives, ketamine and/or lidocaine via IV infusion in adolescents hospitalized secondary to VOC [43]. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist which delivers analgesic effects [44], and has been shown to reduce opioid consumption in a small sample of adolescents hospitalized secondary to VOC [43]. Lidocaine is an amide local anesthetic used for pain control in various diseases and circumstances [43]. Lidocaine, like ketamine, is an NMDA receptor antagonist that delivers an anti-hyperalgesic influence and consequently relieves pain [45]. Puri et al [43] reported reduced opioid consumption during the study period in participants who were administered ketamine or lidocaine. Another alternative to opioids used by individuals with SCD is marijuana. In a qualitative study that examined the management of chronic pain in adults with SCD in the current opioid epidemic, the authors reported that participants offered marijuana as the most common non-opioid pharmacological method used successfully for pain relief [42]. Identifying the optimal mode of administration of marijuana for effective, evidence-based, pain relief must be prioritized, as a recent randomized trial indicated insignificant differences between inhaled marijuana and placebo [46]. Participants in the qualitative study also offered non-pharmacological methods such as warm compresses, praying, music, and acupuncture as pain relief measures to combat SCD pain [42].

To alleviate the current stigma surrounding opioid use in the SCD population, healthcare personnel in emergency departments, and acute care and inpatient settings need to be educated in the management of VOC and the resulting SCD pain. Even when healthcare personnel suspect opioid addiction in patients in VOC, the provision of nursing care should not be averted [47]. The majority of individuals with SCD are non-Hispanic black, and patients seeking pain relief are often viewed as drug-dependent [42, 43], even though CDC data show that prescription opioids such as oxycodone and hydrocodone overdose deaths were the highest among non-Hispanic whites in 2016 [48].

## Conclusion

The need to explore and implement multi-modal (opioid and non-opioid) evidence-based strategies to treat SCD pain exists. This exploration must include an investigation of the ways healthcare personnel can better understand the stigma surrounding opioid treatment and strategies that best facilitate the elimination of observed racial/ethnic inequities in pain management for patients in VOC. We must also consider the lived experiences and perspectives of SCD patients in our efforts to address the opioid crisis. As they experience barriers to effective pain management, increased stigmatization around opioid use, the interference of comprehensive care with provider preoccupation with opioid dosing, and their lack of access to alternative pain management strategies, quality of life is compromised. Our findings provide insight into VOC prescribing practices and highlight a clear need for additional studies examining opioid use in hospitalized adult patients with SCD [42]. Additional randomized controlled trials with comparable comparisons and outcome measures are necessary to form robust conclusions regarding the most effective and least addicting opioid and non-opioid doses for individuals with chronic pain.

## Supplementary Material

**Suppl 1.** Morphine/Morphine Milligram Equivalent Use Among Participants During Hospitalization.

## Acknowledgments

None to declare.

## Financial Disclosure

None to declare.

## Conflict of Interest

None to declare.

## Informed Consent

Not applicable.

## Author Contributions

Concept and design: Osborne. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Osborne. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical or material support: all authors.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## Abbreviations

Hb S: hemoglobin S; MME: morphine milligram equivalent; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; SCD: sickle cell disease; VOC: vaso-occlusive crisis

## References

1. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. Am J Epidemiol. 2000;151(9):839-845.
2. Wang Y, Kennedy J, Caggana M, Zimmerman R, Thomas S, Berninger J, Harris K, et al. Sickle cell disease incidence among newborns in New York State by maternal race/ethnicity and nativity. Genet Med. 2013;15(3):222-228.
3. Dale JC, Cochran CJ, Roy L, Jernigan E, Buchanan GR. Health-related quality of life in children and adolescents with sickle cell disease. J Pediatr Health Care. 2011;25(4):208-215.
4. Hassell KL. Population estimates of sickle cell disease in the US. Am J Prev Med. 2010;38(4 Suppl):S512-521.
5. Darbari DS, Panepinto JA. What is the evidence that hydroxyurea improves health-related quality of life in patients with sickle cell disease? Hematology Am Soc Hematol Educ Program. 2012;2012:290-291.
6. Dobson CE, Byrne MW. Original research: using guided imagery to manage pain in young children with sickle cell disease. Am J Nurs. 2014;114(4):26-36; test 37, 47.
7. Bhatia M, Sheth S. Hematopoietic stem cell transplantation in sickle cell disease: patient selection and special considerations. J Blood Med. 2015;6:229-238.
8. Okam MM, Shaykevich S, Ebert BL, Zaslavsky AM, Ayanian JZ. National trends in hospitalizations for sickle cell disease in the United States following the FDA approval of hydroxyurea, 1998-2008. Med Care. 2014;52(7):612-618.
9. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-1644.
10. Brandow AM, Nimmer M, Simmons T, Charles Casper T, Cook LJ, Chumpitazi CE, Paul Scott J, et al. Impact of emergency department care on outcomes of acute pain events in children with sickle cell disease. Am J Hematol. 2016;91(12):1175-1180.
11. Osborne JC. Quality of life in Latino and non-Latino youth aged 8-18 years with sickle cell disease: a mixed methods study (Doctoral dissertation, Columbia University). 2018.
12. Diggs LM. Anatomic lesions in sickle cell disease. In: Sickle cell disease: diagnosis, management, education, and research. St. Louis: C.V. Mosby. 1973.
13. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood. 2004;103(11):4023-4027.
14. Huntsman RG, Metters JS, Yawson GI. The diagnosis of sickle cell disease in the newborn infant. J Pediatr. 1972;80(2):279-281.
15. Lanzkron S, Carroll CP, Haywood C, Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep. 2013;128(2):110-116.
16. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, Zarkowsky H, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med. 1986;314(25):1593-1599.
17. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, Bemrich-Stolz C, et al. PedsQL sickle cell disease module: feasibility, reliability, and validity. Pediatr Blood Cancer. 2013;60(8):1338-1344.
18. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. Blood. 2012;120(18):3647-3656.
19. Amid A, Odame I. Improving outcomes in children with sickle cell disease: treatment considerations and strategies. Paediatr Drugs. 2014;16(4):255-266.
20. Okpala I, Tawil A. Management of pain in sickle-cell disease. J R Soc Med. 2002;95(9):456-458.
21. Anderson KO, Green CR, Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. J Pain. 2009;10(12):1187-1204.
22. Green CR, Anderson KO, Baker TA, Campbell LC, Decker S, Fillingim RB, Kalauokalani DA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. Pain Med. 2003;4(3):277-294.
23. Bulgin D, Tanabe P, Jenerette C. Stigma of sickle cell disease: a systematic review. Issues Ment Health Nurs. 2018;39(8):675-686.
24. Jacob E, American Pain S. Pain management in sickle cell disease. Pain Manag Nurs. 2001;2(4):121-131.
25. Waldrop RD, Mandry C. Health professional perceptions of opioid dependence among patients with pain. Am J Emerg Med. 1995;13(5):529-531.
26. Burgess DJ, Nelson DB, Gravely AA, Bair MJ, Kerns RD, Higgins DM, van Ryn M, et al. Racial differences in prescription of opioid analgesics for chronic noncancer pain in a national sample of veterans. J Pain. 2014;15(4):447-455.
27. Mossey JM. Defining racial and ethnic disparities in pain management. Clin Orthop Relat Res. 2011;469(7):1859-1870.
28. Rossen LM, Khan D, Warner M. Hot spots in mortality from drug poisoning in the United States, 2007-2009. Health Place. 2014;26:14-20.
29. Bhatt-Poulose K, James K, Reid M, Harrison A, Asnani M. Increased rates of body dissatisfaction, depressive symptoms, and suicide attempts in Jamaican teens with sickle cell disease. Pediatr Blood Cancer. 2016;63(12):2159-2166.
30. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
31. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both

of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-384.

32. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. Can J Ophthalmol. 2008;43(2):180-187.

33. Al-Anazi A, Al-Swaidan L, Al-Ammari M, Al-Debasi T, Alkatheri AM, Al-Harbi S, Obaidat AA, et al. Assessment of patient-controlled analgesia versus intermittent opioid therapy to manage sickle-cell disease vaso-occlusive crisis in adult patients. Saudi J Anaesth. 2017;11(4):437-441.

34. Ballas SK, Bauserman RL, McCarthy WF, Castro OL, Smith WR, Waclawiw MA, Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell A. 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. J Pain Symptom Manage. 2010;40(6):870-882.

35. Desai PC, Brittain JE, Jones SK, McDonald A, Wilson DR, Dominik R, Key NS, et al. A pilot study of eptifibatide for treatment of acute pain episodes in sickle cell disease. Thromb Res. 2013;132(3):341-345.

36. Lagas JS, Wagenaar JF, Huitema AD, Hillebrand MJ, Koks CH, Gerdes VE, Brandjes DP, et al. Lethal morphine intoxication in a patient with a sickle cell crisis and renal impairment: case report and a review of the literature. Hum Exp Toxicol. 2011;30(9):1399-1403.

37. van Beers EJ, van Tuijn CF, Nieuwkerk PT, Friederich PW, Vranken JH, Biemond BJ. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. Am J Hematol. 2007;82(11):955-960.

38. Mikosz CA, Zhang K, Haegerich T, Xu L, Losby JL, Greenspan A, Baldwin G, et al. Indication-specific opioid prescribing for us patients with Medicaid or private insurance, 2017. JAMA Netw Open. 2020;3(5):e204514.

39. Zengin SU, Saracoglu A, Eti Z, Umuroglu T, Gogus FY. The effects of preoperative oral pregabalin and perioperative intravenous lidocaine infusion on postoperative morphine requirement in patients undergoing laparatomy. Pain Res Manag. 2015;20(4):179-182.

40. Centers for Disease Control and Prevention. Calculating total daily dose of opioids for safer dosage. Retrieved on October 14, 2018. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.

41. Volkow ND, McLellan AT. Opioid abuse in chronic pain - misconceptions and mitigation strategies. N Engl J Med. 2016;374(13):1253-1263.

42. Sinha CB, Bakshi N, Ross D, Krishnamurti L. Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: a qualitative study. JAMA Netw Open. 2019;2(5):e194410.

43. Puri L, Morgan KJ, Anghelescu DL. Ketamine and lidocaine infusions decrease opioid consumption during vaso-occlusive crisis in adolescents with sickle cell disease. Curr Opin Support Palliat Care. 2019;13(4):402-407.

44. Luggya TS, Roche T, Ssemogerere L, Kintu A, Kasumba JM, Kwizera A, Tindimwebwa JV. Effect of low-dose ketamine on post-operative serum IL-6 production among elective surgical patients: a randomized clinical trial. Afr Health Sci. 2017;17(2):500-507.

45. Sugimoto M, Uchida I, Mashimo T. Local anaesthetics have different mechanisms and sites of action at the recombinant N-methyl-D-aspartate (NMDA) receptors. Br J Pharmacol. 2003;138(5):876-882.

46. Abrams DI, Couey P, Dixit N, Sagi V, Hagar W, Vichinsky E, Kelly ME, et al. Effect of inhaled cannabis for pain in adults with sickle cell disease: a randomized clinical trial. JAMA Netw Open. 2020;3(7):e2010874.

47. Matthie N, Jenerette C. Sickle cell disease in adults: developing an appropriate care plan. Clin J Oncol Nurs. 2015;19(5):562-567.

48. Centers for Disease Control and Prevention. Annual surveillance report of drug-related risks and outcomes - United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Accessed October 16, 2020. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf.