Published in final edited form as:

Hematol Oncol Clin North Am. 2018 June ; 32(3): 535–550. doi:10.1016/j.hoc.2018.01.014.

Key Components of Pain Management for Children and Adults with Sickle Cell Disease

Amanda M. Brandow, DO, MS¹, Michael R. DeBaun, MD, MPH²

¹Department of Pediatrics, Section of Pediatric Hematology/Oncology Medical College of Wisconsin, Milwaukee, WI, United States

²Department of Pediatrics, Vanderbilt University School of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Synopsis

Sickle cell disease (SCD) pain manifests as severe acute pain episodes and also as a debilitating chronic pain syndrome. Acute pain episodes are the most common reason for health care utilization; however, acute pain episodes are also frequently managed at home. Chronic pain syndrome develops in 30–40% of individuals with sickle cell disease, with increasing incidence and severity with age. We will review critical aspects of pain that are integral to the comprehensive approach to SCD pain management and are rooted in the biopsychosocial model. The review will focus on: opioid pharmacology and psychosocial comorbidities.

Keywords

sickle cell disease; acute pain; chronic pain syndrome; opioids; depression; anxiety; sleep

Background of Individuals with Sickle Cell Disease Pain

Introduction

Acute pain episodes are the most common complication of sickle cell disease (SCD), an inherited hemoglobinopathy affecting over 3 million individuals worldwide.^{1,2} Acute pain episodes are abrupt in onset, unpredictable and account for the majority of health care utilization for SCD; however these episodes are also frequently managed at home.³ Acute pain episodes increase in frequency with age, and a chronic pain syndrome evolves in 30–40% of adolescents and adults with SCD that significantly impairs functioning.^{4,5}

Corresponding Author: Amanda M. Brandow, DO, MS, Department of Pediatrics, Hematology/Oncology, MFRC, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226, abrandow@mcw.edu, Phone: 414-955-4170, Fax: 414-955-6543.

Conflicts of Interest: The authors declare no competing financial interests.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Transition from acute to chronic pain

The abrupt-onset of acute pain episodes commonly occurs in the back, extremities, chest and abdomen.⁶ Temporally associated triggers for pain include, but are not limited to acute infections, dehydration, asthma, cold temperatures and the onset of menstruation; however, often no trigger is identified.^{7–10} Acute pain episodes can start as early as in the first few months of life, increase in frequency with age, and can contribute to the development of a chronic pain syndrome.^{3–5} The biologic basis for acute pain and the emergence of a chronic pain syndrome are likely different. Acute pain is caused by recurrent vaso-occlusion from sickled erythrocytes with resultant ischemia-reperfusion injury, while chronic pain is likely driven by nervous system sensitization.¹¹ Figure 1 depicts the pain trajectory in individuals with SCD.

The diagnosis of a chronic pain syndrome in SCD is challenging, and includes many biologic, psychologic, and sociologic risk factors. Traditionally, chronic pain is defined as pain persisting at least 3–6 months beyond the normal time for healing.¹² This definition often does not apply to individuals with SCD, since SCD pain develops over the lifetime. Evidence-based consensus diagnostic criteria, however, have been established for chronic pain syndrome in SCD.¹³ A key component of these criteria includes: “Reports of ongoing pain on most days over the past 6 months either in a single location or multiple locations”.¹³

Assessment of Individuals with Pain in SCD

No objective measure can assess pain in children and adults with SCD. Thus, the cornerstone of pain management is trust between the affected individual in pain and the health care provider. Pain assessment must incorporate tools that account for the multidimensional aspects of pain. Classic pain assessments use unidimensional measures of pain intensity such as a numeric rating scale, Wong-Baker Pain Scale and Visual Analog Scale.^{14,15} These scales are limited by the momentary assessment of pain and inter-individual variability due to differences in pain tolerance. Thus, the rating on a pain intensity scale should never be the sole determinant for administration of analgesia.

Unfortunately, pain intensity scales do not assess the impact of pain on daily functioning, making them less useful for chronic pain. Instead, patient-reported outcome measures that capture multidimensional aspects of pain and the impact on functioning should be used. These tools include SCD-specific measures (PedsQL SCD Module, Adult Sickle Cell Quality of Life Measurement Information System)^{16,17} and general measures (NIH Patient-reported outcomes measurement information systems- PROMIS).^{18,19} Pain-specific tools with a 7 to 30-day recall period allow for assessment of pain over time and response to treatment.^{16–19} Other multidimensional tools studied in SCD include, but are not limited to, the Youth Acute Pain Functional Ability Questionnaire²⁰, Adolescent and Pediatric Pain Tool²¹, Brief Pain Inventory²² and McGill Pain Questionnaire.²³

Assessment of SCD pain should elicit whether pain is acute, chronic, related to SCD or all three. A clear discussion with the affected individual is required to distinguish between potential types of pain. Pain associated with “overuse syndrome”, which is defined as pain from repetitive motions in daily activities, can be misunderstood and treated as acute SCD

pain, chronic pain syndrome or a prolonged acute pain episode. The temporal association of the new onset of pain coupled with the location and type of pain may help the affected individual and provider distinguish the etiology of the pain. Data show that individuals with SCD use descriptors suggesting both nociceptive (cramping, crushing, tearing, piercing, wrenching) and neuropathic (cold, hot, shooting, stabbing) pain origins.^{24,25} Eliciting pain characteristics and descriptors can improve SCD pain management (see also Chapter 1: Complex pain assessment).

Treatment of Individuals with Pain in SCD

Pain in SCD is complex and includes both acute pain episodes and chronic pain syndromes. We propose, therefore, that management of patients with SCD pain be delivered in the context of the biopsychosocial model, which accommodates the complex interactions that exist among the biological, psychological and social mediators of pain in SCD patients (Figure 2).²⁶ This review will focus on the role of opioid therapy and treatment of psychological co-morbidities; although other areas of pain management including non-pharmacologic strategies and treatment of medical co-morbidities are important, space does not allow for discussion of these additional topics.

Opioid therapy in the context of SCD

After non-pharmacological strategies are used, opioids are currently the mainstay of treatment of patients with SCD pain. Non-opioid medications likely have a role in SCD pain treatment; however, data supporting their use in SCD are limited. Opioid use in SCD should be anchored by an understanding of the neurobiology of pain and pharmacology of analgesia.

Mechanism of action and metabolism of opioids

Opioids bind to the Mu opioid receptors and result in decreased afferent nociceptive input, thereby providing analgesia.²⁷ Knowledge of opioid metabolism is applicable to the use of codeine in SCD. Individuals with SCD have CYP2D6 polymorphisms associated with low enzyme activity. They do not convert codeine into morphine efficiently, and codeine therefore provides less analgesia in them than it would in patients with high CYP2D6 activity.^{28,29} Thus, we do not recommend codeine for routine SCD pain treatment. The FDA issued a contraindication to using codeine in children <12 years and a warning in children 12–18 years who are obese, have obstructive sleep apnea or lung disease.³⁰ These warnings are based on the risk of individuals being ultra-fast codeine metabolizers, which potentiates the rapid conversion to morphine.³⁰ Table 1 outlines pharmacologic properties of selected opioids commonly used in SCD^{31,32}, and should be consulted when selecting an opioid for this population. Morphine and hydromorphone are the most common first-line intravenous opioids used in SCD.^{31,32}

Understanding the therapeutic window of opioids is a fundamental principle required to managing pain in SCD

The pharmacologic principle of placing and keeping an individual in the “therapeutic window” should drive the approach to optimal pain control in individuals with SCD. The

therapeutic window is defined as a range of opioid doses that maximizes the analgesic effect and minimizes side effects^{27,33} (Figure 3). The amount of opioid required to reach the therapeutic window varies based on renal and hepatic function, pharmacokinetics and pharmacodynamics of the opioid, individuals' prior pain events and opioid needs, severity of pain and presence or absence of chronic opioid use.

Once a decision is made to admit an individual for pain management, the choice of opioid, route, frequency and mode of delivery are integral to achieving adequate pain control. To administer an opioid so the desired effect for the drug level stays in the therapeutic window, there should be incremental titration of the opioid dose until effective analgesia is achieved or dose-limiting side effects occur. Once the therapeutic window is achieved, the optimal approach is to administer a continuous opioid infusion, delivered as part of a patient-controlled analgesia (PCA) regimen that allows for patient-initiated "demand" opioid boluses for anticipated breakthrough pain. Our approach is to give all older children and adults with SCD a continuous opioid infusion at the dose designed to provide relief without use of demand doses on the PCA. The PCA bolus dose is based on the pharmacology of the drug every 20 minutes and at 1/6th of the continuous dose. Thus, an individual with an acute pain episode can obtain relief using the PCA and can increase the dose of an hourly infusion by a maximum of 50% when compared to the continuous infusion. Using this outlined algorithm, we have had no significant untoward events over the last two decades. Additional keys to adequate pain management include good nursing care with monitoring for toxicities, having the individual be the only person to push the PCA button, and clear guidelines for increasing and decreasing the basal and PCA opioid dose, while keeping patients in their therapeutic windows.

Opioid delivery via PCA in SCD is associated with decreased length of hospital stay, decreased total opioid consumption and better satisfaction.³⁴ A randomized controlled trial, the IMPROVE trial, sought to compare two PCA dosing regimens (higher demand dose/low constant infusion versus lower demand dose/high constant infusion) on pain control in individuals with SCD. It was, however, terminated early due to poor accrual.³⁵ Thus, a variety of PCA dosing approaches exist. One approach is to divide the total initial amount of opioid required to initially achieve adequate pain control by the number of hours over which the drug was administered. This dose becomes the starting inpatient hourly continuous infusion and the demand dose is 1/6th of the hourly basal infusion set with a 20-minute lockout. During initial management of acute SCD pain, individuals should never be given opioids only as needed ("pro re nata; prn"). The delay in achieving a therapeutic opioid blood level using only prn administration can cause individuals to fall out of the therapeutic window repeatedly and endure undue suffering. When possible, a PCA should be initiated in the acute care setting once a decision is made for admission to decrease the lag time for subsequent opioid doses during transition to the inpatient unit.^{34,36} Routine assessment of pain control is required and PCA dose adjustments should be made as needed. Assessment should include pain intensity measures^{14,15}, functional ability questionnaires²⁰ and other patient-reported outcome measures.^{31,37} If additional demand doses are required more than three times per hour for two hours, the total hourly basal dose should be increased. Figure 3 contrasts two approaches for opioid administration and how each approach impacts time spent within the therapeutic window.

Individuals with SCD can experience opioid tolerance, in which over time incrementally higher opioid doses are required to reach the therapeutic window. This is likely a result of life-long opioid exposure. There is technically no maximum opioid dose so long as there is careful monitoring for toxicity (i.e., somnolence, hypoxia, bradypnea, opioid-induced hypersensitivity, nausea, vomiting, pruritus) and bidirectional communication among all healthcare providers occurs. The goal is to maintain steady pain control and avoid peaks and valleys that remove individuals from the therapeutic window, thereby placing them below the minimum effective concentration (suboptimal pain control) or above the minimum toxic concentration (dose-limiting side effects) (Figure 3).

Home-based SCD pain management

The majority of SCD pain episodes are managed at home.^{4,38} Thus, all individuals should have a personalized home pain management plan. “Pain Action Plans” should be established between individuals and providers as part of optimal SCD care.³⁹ These action plans provide individuals with autonomy to self-manage their pain, helping them to recognize early phases of pain and optimally treat pain at home. Our action plan follows the WHO analgesic ladder for pain management.⁴⁰ When opioids are required, the same pharmacologic principles of placing and keeping the individual in their therapeutic window should guide home management. At the onset of pain, immediate-release opioids (onset of effect: 20–30 minutes) should be used. If age-appropriate, a sustained-release opioid should also be initiated that mimics the continuous intravenous infusion. The combination of long-acting and short-acting opioids provides the optimal approach to keep the individual in the therapeutic window. Pain action plans facilitating home-based management are associated with decreased emergency department visits.⁴¹ Figure 4 depicts two timelines for receipt of analgesia: a perceived standard approach and an empowered approach utilizing a Pain Action Plan.

Psychosocial aspects of SCD pain

Pain management for SCD should use an interdisciplinary team (potential members: hematologist, psychologist/psychiatrist, nurse, social worker, pain medicine specialist) in order to address comprehensively all the somatic and psychosocial aspects of the individual’s pain. The effectiveness of this model in SCD and non-SCD pain conditions has been demonstrated previously.^{42,43}

Association between psychological co-morbidities and SCD pain

A systematic review showed an estimated prevalence of 26% for depression in individuals with SCD⁴⁴ and also a higher prevalence when compared to the general African American population.⁴⁴ Individuals with SCD and depression experience more pain events.^{45,46} In turn, increased SCD pain events are associated with more depression.⁴⁷ Adults with depression have a 2.8 times greater relative risk of increased health care utilization than individuals without depression.⁴⁴ The Pain in Sickle Cell Epidemiology Study (PiSCES) screened 232 individuals for depression and anxiety.⁴⁵ Those with depression reported pain on 71% of days compared to 49% for those without depression,⁴⁵ and individuals with depression reported higher pain intensity and increased pain interference.⁴⁵ Anxiety is also

associated with increased pain. Children with SCD and an anxiety disorder had higher admission rates for pain and longer length of hospital stay.⁴⁸ Adults in the PiSCES study with anxiety reported higher mean pain intensity, pain-related distress, and more opioid usage.⁴⁵ These data underscore the reciprocal relationship between mental health conditions and SCD pain. The long-term effects of treating depression and anxiety on pain will further delineate this relationship.

Assessment of psychological co-morbidities

A comprehensive SCD pain assessment should include depression and anxiety screening in the outpatient clinic, using valid self-reported screening tools to identify individuals at risk. Select tools are outlined in Table 2; many have been used in individuals with SCD.^{44,45} Individuals who have positive screening on self-reported tools require referral to a psychologist/psychiatrist for further evaluation and treatment. In addition to baseline screening, individuals should be screened during episodes of increases in acute pain frequency and opioid needs.

Sleep disturbance and pain in individuals with SCD

Pain can cause sleep disruption, poor sleep quality and difficulty falling and staying asleep.^{49,50} This can decrease pain thresholds and impair endogenous pain inhibitory and coping mechanisms, ultimately exacerbating pain.^{51,52} A study evaluating sleep quality in 328 adults with SCD using the Pittsburgh Sleep Quality index found a 71% prevalence of sleep disturbances.⁴⁶ The individuals with sleep disturbances experienced more days of pain and more frequent acute pain episodes requiring health care utilization.⁴⁶ Another study prospectively assessed the impact of sleep on pain in 74 adults with SCD who completed sleep (duration, fragmentation, continuity) and pain diaries for 3 months.⁵³ Data supported the conclusion that nights with shorter sleep duration, increased fragmentation and less efficient sleep were associated with greater pain severity on the following days.⁵³ Continued research in SCD is needed to determine whether interventions to improve sleep can decrease pain.^{54,55} However, since data strongly support this relationship in non-SCD pain-related disorders, a thorough sleep history should be obtained as part of SCD pain management.⁵⁶

Conclusion

Acute and chronic pain is the most common complication and cause of healthcare utilization in SCD. The pain experience is complex and subjective. Assessment and management of SCD pain should occur in the context of the biopsychosocial model. In SCD, a genetically inherited disease, pain develops over the lifetime of the individual. Thus, this lifelong pain that starts within the first year of life requires comprehensive, interdisciplinary and compassionate care.

Acknowledgements

The authors would like to thank Deva Sharma, MD, Djamila Labib Ghafari, MD and Melissa Day for their critical review of the article.

Funding: National Institutes of Health National Heart, Lung, and Blood Institute 1K23 HL114636-01A1 (AMB)

References

1. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet*. 2013;381(9861):142–151. [PubMed: 23103089]
2. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol*. 2010;85(1):77–78. [PubMed: 20029951]
3. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288–1294. [PubMed: 20371788]
4. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med*. 2008;148(2):94–101. [PubMed: 18195334]
5. Sil S, Cohen LL, Dampier C. Psychosocial and Functional Outcomes in Youth With Chronic Sickle Cell Pain. *Clin J Pain*. 2016;32(6):527–533. [PubMed: 26379074]
6. Ballas SK, Delengowski A. Pain measurement in hospitalized adults with sickle cell painful episodes. *Ann Clin Lab Sci*. 1993;23(5):358–361. [PubMed: 7694538]
7. Smith WR, Bauserman RL, Ballas SK, et al. Climatic and geographic temporal patterns of pain in the Multicenter Study of Hydroxyurea. *Pain*. 2009;146(1–2):91–98. [PubMed: 19683393]
8. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. *J Pediatr Hematol Oncol*. 2006;28(8):481–485. [PubMed: 16912587]
9. Yoong WC, Tuck SM. Menstrual pattern in women with sickle cell anaemia and its association with sickling crises. *J Obstet Gynaecol*. 2002;22(4):399–401. [PubMed: 12521464]
10. Resar LM, Oski FA. Cold water exposure and vaso-occlusive crises in sickle cell anemia. *J Pediatr*. 1991;118(3):407–409. [PubMed: 1999780]
11. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288(5472):1765–1769. [PubMed: 10846153]
12. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156(6):1003–1007. [PubMed: 25844555]
13. Dampier C, Palermo TM, Darbari DS, Hassell K, Smith W, Zempsky W. AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain. *J Pain*. 2017;18(5):490–498. [PubMed: 28065813]
14. Bieri D, Reeve RA, Champion GD, Addicott L, Ziegler JB. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. *Pain*. 1990;41(2):139–150. [PubMed: 2367140]
15. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S240–252. [PubMed: 22588748]
16. Panepinto JA, Torres S, Bendo CB, et al. PedsQL sickle cell disease module: Feasibility, reliability, and validity. *Pediatr Blood Cancer*. 2013;60(8):1338–1344. [PubMed: 23441057]
17. Keller SD, Yang M, Treadwell MJ, Werner EM, Hassell KL. Patient reports of health outcome for adults living with sickle cell disease: development and testing of the ASCQ-Me item banks. *Health Qual Life Outcomes*. 2014;12:125. [PubMed: 25146160]
18. Dampier C, Jaeger B, Gross HE, et al. Responsiveness of PROMIS(R) Pediatric Measures to Hospitalizations for Sickle Pain and Subsequent Recovery. *Pediatr Blood Cancer*. 2016;63(6):1038–1045. [PubMed: 26853841]
19. HealthMeasures: Pain Domains. <http://www.healthmeasures.net/search-view-measures?task=Search.search>. Accessed October 1, 2017.
20. Zempsky WT, O'Hara EA, Santanelli JP, et al. Development and validation of the Youth Acute Pain Functional Ability Questionnaire (YAPFAQ). *J Pain*. 2014;15(12):1319–1327. [PubMed: 25277425]

21. Franck LS, Treadwell M, Jacob E, Vichinsky E. Assessment of sickle cell pain in children and young adults using the adolescent pediatric pain tool. *J Pain Symptom Manage*. 2002;23(2):114–120. [PubMed: 11844631]
22. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 2004;5(2):133–137. [PubMed: 15042521]
23. Melzack R The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1(3):277–299. [PubMed: 1235985]
24. Walco GA, Dampier CD. Pain in children and adolescents with sickle cell disease: a descriptive study. *J Pediatr Psychol*. 1990;15(5):643–658. [PubMed: 2283573]
25. Wilkie DJ, Molokie R, Boyd-Seal D, et al. Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. *J Natl Med Assoc*. 2010;102(1):18–27. [PubMed: 20158132]
26. Taylor LE, Stotts NA, Humphreys J, Treadwell MJ, Miaskowski C. A biopsychosocial-spiritual model of chronic pain in adults with sickle cell disease. *Pain Manag Nurs*. 2013;14(4):287–301. [PubMed: 24315252]
27. Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain*. 2012;6(1):11–16. [PubMed: 26516461]
28. Brousseau DC, McCarver DG, Drendel AL, Divakaran K, Panepinto JA. The effect of CYP2D6 polymorphisms on the response to pain treatment for pediatric sickle cell pain crisis. *J Pediatr*. 2007;150(6):623–626. [PubMed: 17517247]
29. Shord SS, Cavallari LH, Gao W, et al. The pharmacokinetics of codeine and its metabolites in Blacks with sickle cell disease. *Eur J Clin Pharmacol*. 2009;65(7):651–658. [PubMed: 19357842]
30. FDA. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. <https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm>. Accessed October 12, 2017.
31. Brandow AM, Nimmer M, Simmons T, 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. [PubMed: 27517842]
32. Miller ST, Kim HY, Weiner D, et al. Inpatient management of sickle cell pain: a ‘snapshot’ of current practice. *Am J Hematol*. 2012;87(3):333–336. [PubMed: 22231150]
33. Upton RN, Semple TJ, Macintyre PE. Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet*. 1997;33(3):225–244. [PubMed: 9314613]
34. Melzer-Lange MD, Walsh-Kelly CM, Lea G, Hillery CA, Scott JP. Patient-controlled analgesia for sickle cell pain crisis in a pediatric emergency department. *Pediatr Emerg Care*. 2004;20(1):2–4. [PubMed: 14716157]
35. Dampier CD, Smith WR, Wager CG, et al. IMPROVE trial: a randomized controlled trial of patient-controlled analgesia for sickle cell painful episodes: rationale, design challenges, initial experience, and recommendations for future studies. *Clin Trials*. 2013;10(2):319–331. [PubMed: 23539110]
36. Santos J, Jones S, Wakefield D, Grady J, Andemariam B. Patient Controlled Analgesia for Adults with Sickle Cell Disease Awaiting Admission from the Emergency Department. *Pain Res Manag*. 2016;2016:3218186. [PubMed: 27445606]
37. Brousseau DC, Scott JP, Badaki-Makun O, et al. A multicenter randomized controlled trial of intravenous magnesium for sickle cell pain crisis in children. *Blood*. 2015;126(14):1651–1657. [PubMed: 26232172]
38. Dampier C, Ely E, Brodecki D, O’Neal P. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. *J Pediatr Hematol Oncol*. 2002;24(8):643–647. [PubMed: 12439036]
39. Frei-Jones MJ, Ad M.R.. Personal Pain Action Plans for Children and Adolescents with Sickle Cell Disease In: Grasso SDAaKL, ed. *Acute Pain: Causes, Effects and Treatment*: Nova Science Publishers:213–220.
40. WHO’s Cancer Pain Ladder for Adults. <http://www.who.int/cancer/palliative/painladder/en/>. Accessed November 12, 2017.

41. Crosby LE, Simmons K, Kaiser P, et al. Using Quality Improvement Methods to Implement an Electronic Medical Record (EMR) Supported Individualized Home Pain Management Plan for Children with Sickle Cell Disease. *J Clin Outcomes Manag.* 2014;21(5):210–217. [PubMed: 25258504]
42. Powell RE, Lovett PB, Crawford A, et al. A Multidisciplinary Approach to Impact Acute Care Utilization in Sickle Cell Disease. *Am J Med Qual.* 2017;1062860617707262.
43. Brandow AM, Weisman SJ, Panepinto JA. The impact of a multidisciplinary pain management model on sickle cell disease pain hospitalizations. *Pediatr Blood Cancer.* 2011;56(5):789–793. [PubMed: 21370412]
44. Jonassaint CR, Jones VL, Leong S, Frierson GM. A systematic review of the association between depression and health care utilization in children and adults with sickle cell disease. *Br J Haematol.* 2016;174(1):136–147. [PubMed: 26991317]
45. Levenson JL, McClish DK, Dahman BA, et al. Depression and anxiety in adults with sickle cell disease: the PiSCES project. *Psychosom Med.* 2008;70(2):192–196. [PubMed: 18158366]
46. Wallen GR, Minniti CP, Krumlauf M, et al. Sleep disturbance, depression and pain in adults with sickle cell disease. *BMC Psychiatry.* 2014;14:207. [PubMed: 25047658]
47. Edwards CL, Scales MT, Loughlin C, et al. A brief review of the pathophysiology, associated pain, and psychosocial issues in sickle cell disease. *Int J Behav Med.* 2005;12(3):171–179. [PubMed: 16083320]
48. Myrvik MP, Campbell AD, Davis MM, Butcher JL. Impact of psychiatric diagnoses on hospital length of stay in children with sickle cell anemia. *Pediatr Blood Cancer.* 2012;58(2):239–243. [PubMed: 21425450]
49. Onen SH, Onen F, Courpron P, Dubray C. How pain and analgesics disturb sleep. *Clin J Pain.* 2005;21(5):422–431. [PubMed: 16093748]
50. Shaver JL. Sleep disturbed by chronic pain in fibromyalgia, irritable bowel, and chronic pelvic pain syndromes. *Sleep Med Clin.* 2008;3:47–60.
51. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res.* 2001;10(1):35–42. [PubMed: 11285053]
52. Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *Eur J Pain.* 2009;13(10):1043–1047. [PubMed: 19168380]
53. Moscou-Jackson G, Finan PH, Campbell CM, Smyth JM, Haythornthwaite JA. The effect of sleep continuity on pain in adults with sickle cell disease. *J Pain.* 2015;16(6):587–593. [PubMed: 25842346]
54. Lerman SF, Finan PH, Smith MT, Haythornthwaite JA. Psychological interventions that target sleep reduce pain catastrophizing in knee osteoarthritis. *Pain.* 2017;158(11):2189–2195. [PubMed: 28767510]
55. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev.* 2004;8(2):119–132. [PubMed: 15033151]
56. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of P. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133. [PubMed: 27136449]
57. Tanabe P, Myers R, Zosel A, et al. Emergency department management of acute pain episodes in sickle cell disease. *Acad Emerg Med.* 2007;14(5):419–425. [PubMed: 17389246]
58. Tanabe P, Freiermuth CE, Cline DM, Silva S. A Prospective Emergency Department Quality Improvement Project to Improve the Treatment of VasoOcclusive Crisis in Sickle Cell Disease: Lessons Learned. *Jt Comm J Qual Patient Saf.* 2017;43(3):116–126. [PubMed: 28334590]
59. Tanabe P, Hafner JW, Martinovich Z, Artz N. Adult emergency department patients with sickle cell pain crisis: results from a quality improvement learning collaborative model to improve analgesic management. *Acad Emerg Med.* 2012;19(4):430–438. [PubMed: 22506947]

60. Kavanagh PL, Sprinz PG, Wolfgang TL, et al. Improving the Management of Vaso-Occlusive Episodes in the Pediatric Emergency Department. *Pediatrics*. 2015;136(4):e1016–1025. [PubMed: 26391933]
61. Mathias MD, McCavit TL. Timing of opioid administration as a quality indicator for pain crises in sickle cell disease. *Pediatrics*. 2015;135(3):475–482. [PubMed: 25667245]
62. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S454–466. [PubMed: 22588766]
63. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613. [PubMed: 11556941]
64. Saylor CF, Finch AJ Jr., Spirito A, Bennett B. The children's depression inventory: a systematic evaluation of psychometric properties. *J Consult Clin Psychol*. 1984;52(6):955–967. [PubMed: 6520288]
65. Faulstich ME, Carey MP, Ruggiero L, Enyart P, Gresham F. Assessment of depression in childhood and adolescence: an evaluation of the Center for Epidemiological Studies Depression Scale for Children (CES-DC). *Am J Psychiatry*. 1986;143(8):1024–1027. [PubMed: 3728717]
66. Leyfer OT, Ruberg JL, Woodruff-Borden J. Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders. *J Anxiety Disord*. 2006;20(4):444–458. [PubMed: 16005177]
67. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, and Jacobs GA Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.

Key Points

- The optimal management of acute pain episodes and chronic pain syndromes in SCD requires an understanding of the pharmacology principles of pain management.
- Pain management should be delivered using the biopsychosocial model, with interactions between biological, psychological and social influences that contribute to pain addressed.
- SCD pain management should target and keep individuals within the therapeutic window, maximizing analgesic effect and minimizing side effects.
- A complete SCD pain assessment should include screening for depression, anxiety and sleep disturbances.

Figure 1.
Trajectory of pain experience from infancy to adulthood for individuals with SCD.

Figure 2. Biopsychosocial model of pain in individuals with sickle cell disease.

Pain management should be delivered in the context of the biopsychosocial model where interactions between biological, psychological and social influences of pain are addressed.

Figure 3. Different approaches for opioid infusion for inpatient acute SCD pain management.

(A) Continuous opioid infusion with the goal of keeping the individual in the therapeutic window with the addition of breakthrough opioids administered via patient controlled analgesia (PCA) at one sixth the dose of the continuous infusion given every 20 minutes.

Dose adjustment: If the individual self-administers the PCA dose 3 times in consecutive 2 hours, then consider increasing the continuous infusion dose. The new continuous dose should be the equivalence of prior hour's dose (continuous plus cumulative PCA bolus doses). The new PCA dose should be one sixth of the current continuous dose, given every 20 minutes.

(B) Low dose continuous infusion without the goal of infusion being in the therapeutic window. PCA dose is given to put the individual in the therapeutic window. This strategy requires the individual to utilize the PCA throughout the day and night and to awaken at night to relieve pain. There is no strategy to distinguish breakthrough pain from a persistent increase in pain intensity.

Figure 4. Potential timelines of pain treatment for an uncomplicated acute pain event. Two potential timelines for the receipt of analgesia are depicted: (A) Perceived standard approach to acute pain management and (B) empowered approach to acute pain management.

Table 1.

Commonly used opioids for the treatment of individuals with pain from sickle cell disease

Drug	Onset of action Peak Effect	Half life	Dose *	Metabolism	Dose adjustment
INTRAVENOUS					
Morphine	Onset: 5–10 min Peak effect: 20 min	1.5–4 hrs	Intermittent bolus dosing Adults and Pediatrics: 0.1–0.2 mg/kg q2–4 hrs; max dose 10 mg Basal infusion Patient weight <50 kg: Initial: 0.01 mg/kg/hr; dosage range: 0.01 to 0.04 mg/kg/hr Patient weight ≥50 kg: 1–2 mg/hr	Liver	Adjust for liver and kidney disease
Hydromorphone	Onset: 5 min Peak effect: 10–20 min	2–3 hrs	Intermittent bolus dosing Adults: 0.2–1 mg q2–3 hours prn Pediatrics: <50 kg: 0.15 mg/kg q2–4 hrs prn 50 kg: 0.2–0.6 mg q2–4 hrs prn Basal Infusion Adults: 0.5–3 mg/hr Pediatrics: .002–.005 mg/kg/hr	Liver	Adjust for liver and kidney disease
ORAL SHORT-ACTING					
Morphine Immediate Release (IR)	Onset: 30 min Peak effect: 1 hr	Adults: 2–4 hrs Children: 1–3 hrs	Adults: 15 mg q2–4h prn Pediatrics: 0.2 to 0.5 mg/kg/dose q2–4 hours prn; initial maximum dose: 15 to 20 mg (patient weight over 50 kg can use adult dosing)	Liver	Adjust for liver and kidney disease
Oxycodone	Onset: 10 to 15 min Peak effect: 0.5 to 1 hr	2–3 hrs	Adults: 5–15 mg q2–4h prn Pediatrics: 0.1 to 0.2 mg/kg/dose q4h prn	Liver	Adjust for liver and kidney disease
ORAL LONG-ACTING					
Morphine Sustained Release (SR)	Peak effect: 4 hrs		Adults: starting dose is 15 mg q12h Note: Total 24 hr morphine requirements can be given in: 2 divided doses-q12 hrs or 3 divided doses-q 8 hrs Pediatrics: Weight-based dosing: 0.3 to 0.6 mg/kg/dose q12 hrs Fixed dosing: –20 to <35 kg: 10 to 15 mg q8–12 hrs (10 mg tablets not available in US) –35 to <50 kg: 15 to 30 mg q8–12 hrs –50 kg: 30 to 45 mg q8–12 hrs	Liver	Adjust for liver and kidney disease
Oxycodone Extended Release (ER) Note: In United States only Oxycontin™ available	Onset: 40–60 min Peak effect: 3–4 hrs	4.5 hours	Adults: starting dose is 10 mg q12h Pediatrics: Children 11 years and Adolescents: Only recommended for children older than 11 years and taking at least 20 mg of oxycodone or equivalent per day for 2 days prior to starting oxycodone ER. Starting dose is based on current opioid regimen/dosing using the following equation: Dose of oxycodone ER q12 hrs = (mg/day of current opioid X opioid conversion factor)/2	Liver	Adjust for liver and kidney disease

* Starting dose. Titrate up to adequate pain relief.

Data from Lexicomp Online®, Clinical Drug Information, Hudson, Ohio: Lexi-Comp, Inc.; November 8, 2017.

Table 2.

Select self-reported screening tools for depression and anxiety

Tool	Description
Depression	
Beck Depression Inventory (BDI-II) ⁶²	<ul style="list-style-type: none"> • 21 questions • Ages 13 yrs • Assessment of cognitive, affective and somatic symptoms of depression • Questions scored on 0–3 values and summed for total score • Cut-offs indicate minimal, mild, moderate or severe depression (higher scores, more severe depressive symptoms)
Patient Health Questionnaire (PHQ-9) ⁶³	<ul style="list-style-type: none"> • 9 questions • Score 9 of the DSM-IV criteria for depression from 0 (none) to 3 (nearly every day)- depressed mood, sleep issues, anhedonia, poor energy, appetite changes, negative self-image, psychomotor retardation/agitation, poor concentration, self-harm • Score summed: higher scores indicate increased depressive symptoms
Center for Epidemiological Studies-Depression Scale Revised (CESD-R) ⁶²	<ul style="list-style-type: none"> • 20 questions • Measures frequency of symptoms in 9 groups: sadness, anhedonia, appetite, sleep, thinking/concentration, guilt, fatigue, agitation, suicidal ideation • Scores range from 0–60 with higher scores indicating more depressive symptoms; score 16 suggestive of moderate depressive symptoms
CDI-2: Children's Depression Inventory-2 ⁶⁴	<ul style="list-style-type: none"> • Modeled after BDI • 24-item questionnaire • Self-reported scales in 5 areas (negative mood, interpersonal problems, ineffectiveness, anhedonia, negative self-esteem)
Center for Epidemiologic Studies Depression Scale for Children (CES-DC) ⁶⁵	<ul style="list-style-type: none"> • Ages 6–17 yrs • 20 self-report items, scored on 0 (not at all) to 3 (a lot) scale • Scores range from 0–60 with higher scores indicating more depressive symptoms; score 15 suggestive of depressive symptoms
Anxiety	
Beck Anxiety Inventory ⁶⁶	<ul style="list-style-type: none"> • 21 questions • 17 years • Focused primarily on physical symptoms of anxiety (i.e., diaphoresis, dizziness) • Scored 0 (not at all) to 3 (severely); higher scores indicate more anxiety (17–29 moderate, 30–63 severe)
State-Trait Anxiety Inventory ⁶⁷	<ul style="list-style-type: none"> • 40 self-report items (20 items for trait anxiety, 20 items for state anxiety) • 6th grade reading level • Items rated on 0 (almost never) to 4 (almost always) scale; higher scores suggest greater anxiety
State-Trait Anxiety Inventory for Children (STAIC) ⁶⁷	<ul style="list-style-type: none"> • 6–14 years • Similar to adult version • 40 self-report items (20 items for trait anxiety, 20 items for state anxiety)