

## **Topic Brief: Management of Acute Pain Crises in Sickle Cell Disease**

*Below, please find the topic brief prepared by the Addressing Disparities (AD) program on Sickle Cell Disease (SCD). This topic was identified and brought to PCORI by stakeholders in late 2014. We solicited expert input from our colleagues at NHLBI, Michael Engelgau and Harvey Luksenburg. NHBLI is poised to fund 7 consortia focusing on improving quality of care for individuals with SCD. Our goal is to work in partnership with NHBLI to fund a CER trial that complements the work that will be conducted by the 7 consortia.*

### **Contributors**

PCORI Contributors: Mychal Weinert, Randa Abu-Rahmeh, Ayodola Anise, Romana Hasnain-Wynia

#### **1. Overview**

Sickle cell disease (SCD) is a chronic genetic disorder affecting the body's red blood cells (RBCs).<sup>1</sup> It is estimated that between 70,000 and 100,000 Americans, predominately African Americans, have SCD.<sup>2</sup> This disorder affects the hemoglobin in RBCs that is responsible for transporting oxygen from the lungs to the rest of the body.<sup>3</sup> In SCD, the body produces abnormal RBCs that become rigid once they have given up their oxygen and take on a crescent shaped ("sickle") form.<sup>3</sup> The sickled cells clump together, causing blood vessels to become obstructed and consequently reduce blood flow to many parts of the body.<sup>3</sup> This process induces a series of disease-related complications, such as acute chest syndrome and stroke. However, the hallmark complication for patients with SCD is recurrent acute pain episodes, or "pain crises".<sup>2</sup> These episodes are periodic, typically recurrent, and occur throughout life.<sup>4</sup> It is important to note that there are a number of SCD genotypes, each associated with varying clinical severity, which affects the extent to which pain manifests itself.<sup>5</sup>

The management of acute pain is central to the care of SCD; however, it is inadequately addressed across all types of health care settings.<sup>2,8</sup> Individuals with SCD are frequently seen by a primary care physician (PCP) or at community clinics for routine care; however, when suffering from a pain crises, many patients seek treatment in emergency departments (ED).<sup>9</sup> Varying levels of experience in managing pain associated with SCD among both primary care and emergency department physicians lead to inconsistent care and treatment.<sup>10</sup>

Many of the evidence-based guidelines that exist to aid health care professionals in the management of individuals with SCD are based on weak evidence and/or consensus-based opinion, leaving physicians and patients with little information to make informed health care decisions regarding treatment.<sup>2</sup> Additionally, the number of comprehensive centers to treat patients with SCD is sparse. For example, there are approximately 10 comprehensive adult SCD centers in the U.S., compared to 100 centers each for the treatment of hemophilia and cystic fibrosis, which are both less prevalent than SCD.<sup>9</sup>

The primary approach for treating SCD pain focuses on alleviating symptoms with pharmacological agents (i.e., non-opioid and opioid analgesics with or without adjuvants) and replacement of fluids to slow or stop the sickling process.<sup>2,4</sup> However, there is little evidence regarding the type of opioid that should be used.<sup>8,11</sup> Suboptimal trial designs have contributed

to the lack of a strong evidence base.<sup>11</sup> To date, SCD trials suffer from insufficient sample sizes, lack of standardized measures for pain intensity and pain relief, and non-random allocation of patients to study arms.<sup>8, 11</sup> Additionally, while opioid use in the treatment of SCD is frequent, assessing when to prescribe has long been controversial.<sup>7</sup> Physicians do not have reliable guidelines to assess the presence of a pain crisis.<sup>5</sup> The perceived stigma associated with prescribing opioids for SCD also remains a barrier. Fifty-three percent of ED physicians and 23% of hematologists state that more than 20% of their adult patients with SCD are addicted to opioids.<sup>6</sup> However, actual rates of narcotic dependency and abuse are low among patients with SCD.<sup>5</sup>

There is ongoing interest in preventing pain crises in SCD patients through the modification of the underlying pathophysiology.<sup>8</sup> Preventive measures include hydroxyurea treatment and chronic blood transfusions.<sup>8</sup> These two disease modifying therapies are widely available but remain underutilized.<sup>2</sup> Currently, hydroxyurea is the only U.S. FDA-approved disease modifying medication for the treatment of SCD.<sup>12</sup> While hydroxyurea does modify the underlying disease process and reduces the severity and frequency of pain crises, it does not eliminate them.<sup>10</sup>

Hydroxyurea treatment and some improvements in general supportive care have increased the average lifespan of children with SCD to live past adolescence.<sup>13</sup> However, SCD-related mortality rates are highest among young adults transitioning from pediatric to adult care and there are no established evidence-based guidelines for facilitating this transition.<sup>14</sup>

## **2. Patient-Centeredness**

Studies show that patients and clinicians are dissatisfied with the quality of SCD pain management.<sup>9</sup> Recent literature documents that SCD patients report: not having enough involvement in decisions about their own care, poor pain management, lack of access to outpatient care services, poor communication between health care professionals, and inadequate follow-up.<sup>9, 10</sup>

## **3. Impact (Burden) of the Condition**

Approximately 73.1 out of 1,000 newborn African Americans in the United States are born with SCD.<sup>15</sup> Despite some improvements in care, the average lifespan ranges between 36 and 53 years for men, and 39 and 56 years for women.<sup>3</sup>

Nearly all individuals with SCD will suffer from an acute pain crisis in their lifetime, accounting for approximately 90% of their hospital admissions.<sup>2, 8</sup> In the “Pain in Sickle Cell Epidemiology Study (PiSCES)”, adults who completed the daily diary entries reported pain on 54.5% of the 31,017 days surveyed.<sup>15</sup>

By the time a patient with SCD reaches age 45, he/she will have accrued over \$900,000 in undiscounted medical expenses.<sup>16</sup> Eighty percent of the medical costs accrued by patients with SCD are associated with hospitalization, suggesting that interventions to reduce complications, such as pain crises, could be cost-saving.<sup>16</sup> In addition to the economic repercussions, those suffering from SCD pain also face emotional, behavioral, and psychological difficulties.<sup>8</sup>

#### 4. Evidence Gaps

General Guidelines for Pain: The National Heart, Lung, and Blood Institute (NHLBI) released an expert panel report in 2014 on “Evidence-Based Management of Sickle Cell Disease.”<sup>2</sup> The report highlights that appropriate management of acute pain crises is central to the care of individuals with SCD.

- The evidence-based recommendations made by the panel in regards to pharmacologic treatment are as follows:
  - **Strong Recommendations with High-Quality Evidence:**
    - Rapidly initiate treatment with parenteral (injected) opioids for severe pain.
  - **Moderate Recommendations with Low-Quality Evidence:**
    - Continue treatment with NSAIDs in patients with mild to moderate pain who report relief with NSAIDs.
    - Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus “as requested” administration.
    - Do not administer a blood transfusion unless there are other indications for transfusion.
- Many recommendations (consensus-panel expertise) included **practices that have not yet been validated by evidence**, but are currently in use. Some of these recommendations include:
  - Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration.
  - Use an individual prescribing and monitoring protocol or an SCD-specific protocol wherever possible to promote rapid, effective, and safe analgesic management and resolution of the pain crisis.
  - Administer oral NSAIDs as an adjuvant analgesic in the absence of contraindications.
  - Use adjunctive non-pharmacologic approaches to treat pain such as local heat application and distraction.

Analgesic Treatment for Pain: A 2014 Cochrane systematic review assessed the effectiveness of pharmacological analgesic interventions for pain management, including the treatment of acute and chronic pain in children and adults.<sup>8</sup>

- Nine RCTs of analgesic use in SCD patients suffering from acute pain crises were identified, however the sample sizes in these trials were small.
  - No studies addressed the efficacy of acetaminophen or weak opioids.
  - There was some evidence that suggested that NSAIDs given by injection can reduce pain.
  - One study demonstrated that morphine given orally was as effective as by morphine given by injection.

- Lack of data, small patient numbers, variations in study design and outcome measures limit the review.
- Overall, there was **insufficient evidence** to determine the effectiveness of pharmacological analgesic interventions for pain management in SCD.
- The review called for the following when designing future studies:
  - More multi-center trials to ensure sufficient recruitment for adequately powered studies.
  - A standardized protocol of pain management as the basis for control arms.
  - Standardized measures of pain intensity and pain relief to facilitate the comparison between studies.
  - Appropriate outcome measures that are relevant to patients and families.

Psychological Treatment for Pain: A 2015 Cochrane systematic review examined the evidence for psychological interventions to improve the ability of people with SCD to cope with their condition and related pain.<sup>17</sup>

- Seven RCTs were eligible for inclusion in the review. Only five studies, with a total of 260 participants, provided suitable data to be entered into the review.
  - One study suggested that cognitive behavioral therapy (CBT) helped with pain management but not the sensory aspect of pain intensity.
- **There was insufficient evidence** to draw strong conclusions about the efficacy of psychological interventions for patients with SCD. The review called for the following:
  - Further research using a structured approach to assess psychological therapies, taking into account clinical and demographic variables.
  - Well-designed and adequately powered studies that incorporate treatment manuals to promote consistency and allow for replication.
  - Future studies that identify the most important components of psychological interventions for the SCD community.

Fluid replacement for Pain: A 2015 Cochrane systematic review sought to examine randomized controlled trials (RCTs) that demonstrated the best approaches for replacing fluids, however no such trials were found.

- Due to **insufficient evidence**, the authors concluded that a large, multi-center trial is needed to fill evidence gaps regarding fluid replacement for individuals with SCD.

Hydroxyurea: A systematic review published in 2008, commissioned by the National Institutes of Health Office of Medical Applications of Research, assessed the efficacy, effectiveness, and toxicity of hydroxyurea when used to treat adults with SCD.<sup>12</sup>

- A single RCT tested the efficacy of hydroxyurea in adults with SCD.
  - The high-quality, multicenter trial enrolled 299 adults.
  - The primary endpoint was the reduction in the frequency of painful crises.
  - The median number of painful crises was 44% lower than the placebo group.
  - The time to first painful crisis was three months compared to 1.5 months in the placebo group.

- Costs for hospitalization for pain were significantly lower in the hydroxyurea group.
- There is **strong evidence** that the use of hydroxyurea has a positive effect on the frequency and severity of pain crises.

Barriers to Appropriate Care: A 2009 systematic review examined interventions to approve appropriate use of therapies for SCD treatment, focusing on appropriate pain management during pain crises.<sup>18</sup>

#### **Barriers**

- Thirteen studies identified patient and provider related barriers for appropriate pain management during pain crises.
- The most common barriers identified by both patients and providers were negative provider attitudes (n=13) and lack of provider knowledge (n=5). Negative provider attitudes included:
  - Not believing that patients were genuinely in pain,
  - Being suspicious of drug abuse or addiction,
  - Stigmatization of patients with SCD,
  - Insensitivity or lack of sympathy, and
  - Unspecified negative perceptions or attitudes.
- There is **strong evidence** that negative provider attitudes and poor provider knowledge are barriers to use of appropriate pain medications during pain crises for patients with SCD.

Transition to Adult Care: A 2012 systematic review conducted by the Sickle Cell Disease Association of America examined barriers to and approaches for successful transition of patients with SCD from adolescent to adult care.<sup>19</sup>

- 14 studies were reviewed:
  - Four studies explored factors directly attributable to adolescence during the time of transition, such as transition readiness.
  - Three studies observed the patient's status shortly after transition.
  - Three studies identified systemic or patient-related factors that can interrupt the transition process (i.e., provider knowledge and patient education).
  - Four studies proposed model programs to inform better management approaches.
- The review recommended the following based on **limited evidence**:
  - Patient-centric transition plans to be implemented in pediatric facilities that allow for:
    - Enough flexibility to accommodate individual patient needs,
    - Patients to explore their opportunities for independence and to develop skills in managing SCD,
    - Parents and caregivers to be actively involved, and
    - The inclusion of pediatric and adult physicians, nurse practitioners, social workers, education coordinators, and clinical psychologists.

## 5. Ongoing Research

There are currently 41 ongoing studies listed on ClinicalTrials.gov using the search terms “sickle cell disease” and “pain.” There is also one ongoing study listed on ClinicalTrials.gov using the search terms “sickle cell disease” and “transition to adult care”. Studies with unknown status were excluded in the initial search. Twenty-three studies were excluded due to lack of relevance, duplicate listings, or because they were being conducted outside the US. While international studies were excluded from this topic brief, leveraging findings from countries where SCD is more prevalent (e.g., Nigeria), may provide valuable information that could be applied in the U.S. setting.

- Almost all studies currently taking place are Phase 0-4 RCTs (n=15), or observational (n=1). See “Table 1: Ongoing Trials in ClinicalTrials.Gov.”
  - There are no current head-to-head comparative effectiveness research (CER) trials comparing pain treatments for persons with SCD.
  - The majority of RCTs are focusing on new drugs for the treatment of pain in SCD.
  - One Phase 4 study is assessing two ways to treat pain crises (standardized, weight-based dosing with opioids vs. patient specific dosing) to determine if a large RCT is feasible.

PCORI is currently funding two studies on SCD.

- [One study](#) is measuring the effectiveness of a decision aid for therapeutic treatment options. (Funded in 2013, concluding in 2016)
- [Another study](#) is comparing patient-centered outcomes in the management of pain between emergency departments and dedicated acute care facilities for adults with SCD. (Funded in 2014, concluding in 2017)

## 6. Likelihood of Implementation of Research Results in Practice.

Current practices for treatment of SCD are being used with limited evidence. This gap in the evidence base needs to be addressed as clinicians and patients are seeking guidance about treatment options to inform decision-making regarding the treatment of SCD to improve outcomes.

## 7. Durability of Information

Well-designed studies are needed and can have lasting benefit.

## 8. Potential Research Questions

- What is the comparative effectiveness of different models of care for children with SCD transitioning from pediatric to adult care?
- What is the comparative effectiveness of different approaches to facilitate better management and improve patient-centered and clinical outcomes during transition from pediatric to adult care taking into consideration patient and family, clinician, health system, and community factors?

- What is the comparative effectiveness of interventions to improve the treatment and management of acute pain crises in patients with SCD?

NHLBI released a funding announcement entitled “Using Implementation Science to Optimize Care of Adolescents and Adults with Sickle Cell Disease” in July 2015. Applications are due October 2015 and awards to seven geographically diverse sites will be made in the first quarter of 2016. The AD program is seeking to explore opportunities for collaboration with NHLBI. Pending approval from the SOC, PCORI will have further discussions with NHLBI on this effort including the development and refinement of key patient-centered CER questions that will complement NHLBI’s current efforts.

---

## References

1. Molter BL, Abrahamson K. Self-Efficacy, Transition, and Patient Outcomes in the Sickle Cell Disease Population. *Pain Management Nursing: Official Journal Of The American Society Of Pain Management Nurses*. 2014. PubMed PMID: 25047808.
2. U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute. *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report*, 2014.
3. Cho G, Hambleton IR. Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. *The Cochrane database of systematic reviews*. 2014;1:CD008360. PubMed PMID: 24399756.
4. Okomo U, Meremikwu MM. Fluid replacement therapy for acute episodes of pain in people with sickle cell disease. *The Cochrane database of systematic reviews*. 2015;3:CD005406. PubMed PMID: 25764071.
5. Lovett PB, Sule HP, Lopez BL. Sickle Cell Disease in the Emergency Department. *Emergency Medicine Clinics of North America*. 2014 8/1/August 2014;32:629-47. PubMed PMID: S0733862714000352.
6. Smith WR. Treating Pain in Sickle Cell Disease with Opioids: Clinical Advances, Ethical Pitfalls. *Journal of Law, Medicine & Ethics*. 2014 06//;42(2):139-46. PubMed PMID: 97071843.
7. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, et al. Daily assessment of pain in adults with sickle cell disease. *Annals Of Internal Medicine*. 2008;148(2):94-101. PubMed PMID: 18195334.
8. Dunlop R, Bennett Kyle CLB. Pain management for sickle cell disease in children and adults. *Cochrane Database of Systematic Reviews* [Internet]. 2014; (4). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003350.pub3/abstract>.
9. Lanzkron S, Carroll CP, Hill P, David M, Paul N, Haywood C, Jr. Impact of a dedicated infusion clinic for acute management of adults with sickle cell pain crisis. *American Journal Of Hematology*. 2015;90(5):376-80. PubMed PMID: 25639822.
10. Raphael JL, Oyeku SO. Sickle cell disease pain management and the medical home. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2013;2013:433-8. PubMed PMID: 24319216. Epub 2013/12/10. eng.
11. Dampier CD, Smith WR, Wager CG, Kim H-Y, Bell MC, Miller ST, 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. *Clinical trials (London, England)*. 2013;10(2):319-31. PubMed PMID: 23539110.

12. Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, et al. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. *Annals Of Internal Medicine*. 2008;148(12):939-55. PubMed PMID: 18458272.
13. Crosby LE, Quinn CT, Kalinyak KA. A Biopsychosocial Model for the Management of Patients With Sickle-Cell Disease Transitioning to Adult Medical Care. *Advances in therapy*. 2015 04/02;32(4):293-305. PubMed PMID: PMC4415939.
14. DeBaun MR, Telfair J. Transition and Sickle Cell Disease. *Pediatrics*. 2012 November 1, 2012;130(5):926-35.
15. Ojodu J, Hulihan MM, Pope SN, Grant AM. Incidence of sickle cell trait--United States, 2010. *MMWR Morbidity and mortality weekly report*. 2014 Dec 12;63(49):1155-8. PubMed PMID: 25503918. Epub 2014/12/17. eng.
16. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. *American Journal of Hematology*. 2009;84(6):323-7.
17. Anie Kofi A, Green J. Psychological therapies for sickle cell disease and pain. *Cochrane Database of Systematic Reviews [Internet]*. 2015; (5). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001916.pub3/abstract>.
18. Haywood C, Jr., Beach MC, Lanzkron S, Strouse JJ, Wilson R, Park H, et al. A systematic review of barriers and interventions to improve appropriate use of therapies for sickle cell disease. *Journal Of The National Medical Association*. 2009;101(10):1022-33. PubMed PMID: 19860302.
19. Jordan L, Swerdlow P, Coates TD. Systematic review of transition from adolescent to adult care in patients with sickle cell disease. *Journal of pediatric hematology/oncology*. 2013 Apr;35(3):165-9. PubMed PMID: 23511487. Epub 2013/03/21. eng.

Table 1: Ongoing Trials in ClinicalTrials.Gov

Study	Intervention	Type	Completion Date	Location	Sample Size	Funder
Pain Management in Children and Young Adults With Sickle Cell Disease	Gabapentin vs. Placebo	Phase 2	October 2017	St. Jude Children's Research Hospital	190	Scan   Design Foundation
Comparing Acute Pain Management Protocols for Patients With Sickle Cell Disease	Compare two ways to treat pain crises (standardized, weight-based dosing vs. patient specific dosing) in the ED for adults with sickle cell disease, and to determine if a large randomized controlled trial is feasible and required.	Phase 4 (Pilot Study)	September 2016	Duke University	77	NHLBI
Methadone in Pediatric and Adult Sickle Cell Patients (MSCD)	Methadone vs. Standard of Care	Efficacy study	September 2015	Washington University School of Medicine	54	Not listed
MBSR for Pain Catastrophizing in SCD*	Mindfulness-based Stress Reduction	Exploratory; Feasibility study	August 2016	Duke University	60	NIH; NINR
Vaporized Cannabis for Chronic Pain Associated With Sickle Cell Disease (Cannabis-SCD)*	Cannabis vs. Placebo	Phase 1/ Phase 2	March 2016	University of California, San Francisco	35	NHLBI
Study of SANGUINATE™ In the Treatment of Sickle Cell Disease Patients With Vaso-Occlusive Crisis	SANGUINATE vs. Placebo	Phase 2	April 2016	Prolong Pharmaceuticals	24	Prolong Pharmaceuticals

Study	Intervention	Type	Completion Date	Location	Sample Size	Funder
Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease	Rivipansel vs. Placebo	Phase 3	July 2018	Pfizer	350	Pfizer
Music Therapy in Sickle Cell Pain Mixed Methods Study	Music Therapy vs. Music Listening vs. Control (standard of care)	Exploratory/Feasibility Study	June 2016	University Hospital Case Medical Center	120	Kulas Foundation
Safety Of Rivipansel (GMI-1070) In The Treatment Of One or More Vaso-occlusive Crises In Hospitalized Subjects With Sickle Cell Disease	Single group assignment to Rivipansel	Phase 3	February 2020	Pfizer	250	Pfizer
Ketamine Infusion for Acute Sickle Cell crisis in the Emergency Department (KISS)	Ketamine vs. Placebo (Saline)	Safety/Efficacy Study	January 2017	Billy Sin	106	Not listed
Use of a Mobile-based App for SCD Patients (SMART)	Collect information about differences in the use of two traditional pain assessment modes (verbal scale and paper) versus the use of a pain assessment tool on a mobile device in the form of a smartphone, tablet, or iPad with an Android or iOS operating system.	Observational	June 2015	Duke University	100	Not Listed
Intravenous Gammaglobulin for Sickle Cell Pain Crises	Immune Globulin Intravenous vs. Placebo (Saline)	Phase 1/Phase 2	December 2014	Albert Einstein College of Medicine of Yeshiva University	60	Not Listed

Study	Intervention	Type	Completion Date	Location	Sample Size	Funder
Effect of Simvastatin Treatment on Vaso-occlusive Pain in Sickle Cell Disease	Single group assignment to Simvastatin	Phase 2	June 2015	Children's Hospital & Research Center Oakland	25	Not Listed
Inhaled Mometasone to Reduce Painful Episodes in Patients With Sickle Cell Disease (IMPROVE)	Mometasone Furoate vs. Placebo	Phase 2	February 2017	Jeffrey Glassberg, Mount Sinai School of Medicine	45	Not Listed
Apixaban in Patients With Sickle Cell Disease	Apixaban vs. Placebo	Phase 3	December 2015	Nirmish Shah, Duke University Medical Center	60	Bristol-Myers Squibb
Nitrous Oxide Analgesia Vaso-occlusive Crisis	Single group assignment to Nitrous Oxide	Phase 2	June 2015	Columbia University	12	Not Listed
Patient-Provider Tools to Improve the Transition to Adult Care in Sickle Cell Disease (iTransition)	Compares a chronic disease self-management program to a patient portal intervention (MyChart for SCD Intervention).	Interventional	July 2015	Children's Hospital Medical Center, Cincinnati	85	Children's Hospital Medical Center, Cincinnati