



National Institutes of Health

# Approaches to Effective Therapeutic Management of Pain for People with Sickle Cell Disease

## Executive Summary



# Approaches to Effective Therapeutic Management of Pain for People With Sickle Cell Disease (SCD)

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## Co-leads

National Center for Complementary and Integrative Health (NCCIH) and National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

## NIH collaborators

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute on Drug Abuse (NIDA), National Institute on Minority Health and Health Disparities (NIMHD), National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Nursing Research (NINR)

## Executive Summary

NIH held this workshop to present and discuss the current state of the science on acute and chronic SCD pain pathophysiology, address challenges and opportunities in SCD pain management, and develop strategies to optimize SCD pain management. In **introductory remarks on Day 1**, NCCIH Director Dr. Helene Langevin emphasized that advancement of research on sickle cell pain requires improved understanding of both the vaso-occlusive crisis and of the chronic pain some people with SCD experience between crises. NIH Director Dr. Francis Collins said that SCD, which affects 100,000 Americans, is a critically important condition for NIH research. Much remains to be learned about SCD pain, including why people who have had curative therapies may not be pain-free.

In his **Day 1 keynote address**, Dr. Wally Smith of Virginia Commonwealth University reminded attendees that the pain experience should be reconceptualized as a biopsychosocial phenomenon, not as a simple, Cartesian biological response to an external stimulus. Melzack's pain neuromatrix model, which theorizes multiattribute biopsychosocial pain inputs and pain expressions, may be particularly relevant to SCD pain. SCD pain is underappreciated and greatly affects quality of life. Sufferers are stigmatized, and current therapies are woefully insufficient.

Speakers and panelists in **Expert Group 1 – Biology of SCD Pain** explained that vaso-occlusion in SCD probably results from abnormal adhesion of all blood elements to each other and to endothelial cells. Ubiquitous, subclinical, fluctuating vaso-occlusion generates and reflects inflammation. Painful responses therefore fluctuate in frequency and intensity. Moreover, research in humanized sickle mice suggests that prior nerve injury may contribute to pain persistence even after curative therapies. Central neuropathic pain, denoted by increased connectivity between the default mode network and the anterior insula, a phenomenon also observed in people with other conditions involving chronic pain, has been observed in SCD patients. People with SCD often have cognitive changes; the relation of these changes to pain

is unclear. Mechanisms involving inflammation of myofascial trigger points may contribute to SCD pain. Muscle spasms are an overlooked and undertreated source of pain in SCD. Major knowledge gaps identified by this group include the need for improved pain phenotyping, better methods for measuring effects of cognition on pain, and a better understanding of musculoskeletal pain in SCD. Tools and resources to fill research gaps include technology-based interventions and pain quantification, greater access to human patient tissues including organ donations, and appropriate knockout mice.

Speakers and panelists in **Expert Group 2—Psychosocial and Environmental Factors Impacting SCD Pain** emphasized the bidirectional influences between SCD pain and psychological functioning, and between pain and sleep. SCD pain not only can contribute to a variety of long-lasting psychosocial consequences in youth and adults, but also can affect the psychological well-being of caregivers and family members. Partly because these related therapeutic targets are vastly underrecognized, psychological and sleep interventions are underused for SCD pain. Further, the social and ecological contexts surrounding acute and chronic SCD pain often are ignored in conceptual frameworks and theoretical models, though interventions to address these factors may be the most important. For example, more research is needed on the impact of SCD pain on socioeconomic outcomes and on the roles financial hardship and discrimination may play in pain. Knowledge gaps identified by this group include inadequate information about predictors of poor pain outcomes, risk factors for the transition from acute to chronic pain, the impact of negative experiences on the pain cycle, the temporal order of pain and psychosocial consequences, and the experiences of patients who have shown resilience to SCD pain. Needed resources include more funding to support multisite longitudinal studies that focus on the patient experience. Also, the field is underresourced in terms of genome-wide association studies (GWAS) because African Americans are not adequately represented.

Speakers and panelists in **Expert Group 3—Genetics/Microbiome Factors Impacting SCD Pain** said that microbiome alterations play a role in some chronic inflammatory diseases and pain-related disorders and are being investigated in SCD. Pain-related candidate gene polymorphisms have been identified in SCD patients. Epigenetic studies on chronic pain are in their early stages. Knowledge gaps include a lack of understanding of how all these factors relate to different pain phenotypes. Because SCD is relatively uncommon, large GWAS studies may not be possible. Instead, reliable, relevant, acceptable animal models are needed. Resources needed to fill knowledge gaps include consistent definitions of acute and chronic pain to facilitate identification of genotype-phenotype associations, as well as data on genomic and social determinants of SCD pain.

Dr. Lakiea Bailey of the Sickle Cell Consortium provided a **patient perspective**, noting that SCD patients learn to live with pain, but it affects every aspect of their lives. Poor care is common and may prompt people to manage even severe, acute pain at home because that is less objectionable than going to the emergency room.

**Roundtable Discussion 1** summarized survey responses from the workshop participants, who agreed that more investment is needed in research on SCD pain. Technologies developed in other areas should be leveraged in SCD. More interaction among researchers, health professionals, and patients is needed.

In **introductory remarks on Day 2**, NHLBI Director Dr. Gary Gibbons said that improved treatments for SCD have led to increases in life expectancy, but improvements are also needed in pain management, quality of life, and emergency department care for people with SCD. NHLBI is committed to pursuing a research agenda that will advance pain management and eventually improve access to curative therapies for SCD. Dr. Rebecca Baker, director of the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, explained that the NIH HEAL Initiative's focus on the twin epidemics, first of opioid misuse and opioid-related mortality, and second of chronic pain, includes planned multisite trials of nonopioid pharmacologic or nonpharmacologic approaches for SCD pain, as well as implementation science studies, both to improve use of evidence-based interventions and to address structural barriers such as stigma and racism that hinder effective SCD pain management.

In her **Day 2 keynote address**, Dr. Cheryl Stucky of the Medical College of Wisconsin reviewed the issues discussed the previous day, shared data showing disproportionately lower funding for SCD research compared to cystic fibrosis research, and emphasized that clinicians need to consider the whole person and that person's context to understand individual differences in the pain experience. Clinicians need to trust people with SCD, believe their pain experience, and empathize with their circumstances.

Speakers and panelists in **Expert Group 4—Measuring Pain and Sequelae in Patients for Clinical Trials** explained that most research on drugs for SCD pain has focused on acute pain; chronic pain should also be studied. Similarly, most outcomes measured in SCD clinical trials have excluded multiple related pain descriptors and features, as well as sleep, fatigue, and physical function, each of which is related to pain. Researchers highlighted how vasoconstriction contributes to SCD pain and vaso-occlusive crises and can be used as an objective biomarker to study responses to experimental pain. Further, people with SCD differ significantly from controls in their sensitization to mechanical pain stimuli. Researchers emphasized that clinical trials of interventions for SCD pain should choose participants based on pain phenotyping. For example, the U.S. Food and Drug Administration's established endpoints for SCD clinical trials research include patient-reported endpoints and outcomes for pain, affect, and function. Similarly, many of the outcome measures in the PhenX Toolkit and database can be used in SCD and are currently being further customized for SCD. The Patient-Reported Outcomes Measurement Information System (PROMIS) measures useful pain-related domains for both children and adults. Researchers should measure intraindividual variability in such measures to delineate pain phenotypes in SCD. Research should also measure pain and pain phenotype transformation throughout the lifespan. Further, researchers should use qualitative research methods to deepen understanding of the lived experience of SCD pain. Ecological momentary assessment methods can help to reduce bias. Wearable devices can be useful, but the validity of their measurements must be assessed.

Speakers and panelists in **Expert Group 5—Current or Promising Treatments for Acute and Chronic SCD Pain** noted that strategies for treating acute pain in SCD are in place, but strategies for treating chronic pain are not. The evidence base for nonpharmacologic interventions is not very rigorous. Preliminary studies suggest that acupuncture, massage, yoga, guided relaxation, mindfulness-based interventions, biofeedback, and aquatic rehabilitation may each be helpful. Cognitive behavioral therapy for insomnia may improve sleep and therefore pain. Ultrasound modulation and synthesized cannabinoids may be useful. Research on gene therapy is in its early stages, but the impact on pain seems promising. Some patients who have received stem cell transplants continue to experience pain. Potential

mechanisms for this pain may include opioid-induced hyperalgesia, central sensitization, genetic variability, and SCD-related organ damage such as avascular necrosis of hips, knees, and shoulders; spine bone necrosis; and leg ulcers. Interventions to address environmental exposures such as racism and discrimination as well as socioeconomic disadvantage may have profound impacts on the pain experience.

Speakers and panelists in **Expert Group 6—Overcoming Challenges of Evidence-Based Pain Management: Patient Engagement, Stigma, Bias, and Access to Quality Care**

observed that emergency department care for SCD pain needs improvement despite the existence of evidence-based guidelines. Care for SCD pain at SCD-specific infusion centers is much better, but the majority of patients do not have access to these infusion centers. Those involved in health care and research should be social justice advocates for optimal outcomes for all patients. More emphasis should be given to the social variables within the biopsychosocial pain model and to treating patients with empathy. Further, the transition from (usually adequate) pediatric to (often absent or substandard) adult care poses enormous challenges for people with SCD. Often, adolescents with SCD do not find an adult SCD provider and/or become less engaged in their own care. The HIV literature is a good source of information for evidence-based interventions aimed at reducing bias, stigma, and discrimination. Palliative care can be helpful for people with SCD, but not enough providers are available, and SCD patients are sometimes excluded from palliative care because of their longer life expectancy.

Ms. Shauna Whisenton of the American Society of Hematology Research Collaborative provided a **patient perspective** from her viewpoint as a hematopoietic stem cell transplant recipient. As is true for many people with SCD, her symptoms worsened as she matured, leading to frequent hospitalizations, the need for pain medication, increased experiences with stigma, and a decline in her overall health. Even after her transplant, which she envisioned would be the end of her struggles, recovery was prolonged and difficult, with multiple complications and difficulty in finding opioid detoxification because many rehabilitation facilities would not admit her.

Participants in **Roundtable Discussion 2** suggested that many potential interventions applicable to the SCD pain field are not yet ready for large clinical trials. Barriers to readiness include improvement in pain phenotyping, more specification and evidence supporting current treatment guidelines, more and more detailed and multifaceted pain measurement tools, and development of SCD patient registries. Survey responses indicated that bias, racism, disparities, and lack of access to health care providers and therapies are the chief barriers to care. Insurance coverage for nonpharmacologic interventions is essential to their implementation. Partnerships with community and religious organizations can increase dissemination of information about SCD.

In **closing remarks**, Dr. Monica Webb Hooper, deputy director of the National Institute on Minority Health and Health Disparities, noted the importance of health disparities and stigma in SCD and said that they should be discussed when planning SCD pain management strategies. A health equity lens must be applied to the problem of pain in SCD. To advance the care of patients, intentional assurances of equity must be included at the beginning of research efforts, with a clear plan for intervention implementation.