Sickle Cell Pain and Opioids: NASEM Analysis of Gaps in Research

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• No off-label drug use will be mentioned in this presentation.

• Emmaus Pharmaceuticals—consultant, investigator
• Global Blood Therapeutics—consultant
• Health Resources and Services Administration—investigator
• Incyte Corporation—investigator
• Ironwood Pharmaceuticals—consultant
• Modus Therapeutics—consultant
• National Heart Lung and Blood Institute, National Institutes of Health—investigator
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Sickle Cell Disease Acute Pain: Phenotypic Features

- Rare Autosomal Recessive Hemoglobinopathy (100,000 in US)
- Vaso-occlusive (VOC=vaso-occlusive crisis)
- Nociceptive
- Ischemic and inflammatory
- Acute or acute-on-chronic
- Multi-local
Acute SCD Pain: AAAPT Definition--2018

- Patient with SCD by lab testing, plus
- Lasts at least 2 hours
- Started in last 10 days
- One physical sign (palpation, movement cause pain, or decreased ROM)
- Can’t be explained by SCD complication (leg ulcer, priapism, edema, bone infarction, AVN, osteo, hepatobiliary)

Subtypes
- 1- No painful comorbidity
- 2- With painful comorbidity

- May occur with or without chronic SCD pain
- Occurs more often with chronic SCD pain

Eligible Studies reviewed
- 32 RCTs with more than 1,800 people of all ages
- 34 observational studies
- 30 case reports

Highest quality evidence, strongest recommendation for opioids within 30-60 minutes of arrival in the Emergency Department.
- Evidence from several RCTs and observational studies supports opioids for VOCs.
- Indirect, high-quality evidence from populations without SCD also supports opioids for VOCs.

RCTs and observational studies support NSAIDs, were conflicting, but reduced pain decreased LOS

Several RCTs and observational studies support the use of around-the-clock dosing vs intermittent for inpatient VOCs.

Chronic SCD Pain: Phenotypic features

• Types of Evidence
  – Patient-reported Descriptor evidence
  – Quantitative Sensory Testing evidence
  – Functional Magnetic Resonance Imaging evidence

• Features similar to those found in conditions exhibiting central sensitization
  – Fibromyalgia
  – Irritable Bowel Syndrome
  – Chronic Low Back Pain
  – Chronic headache
SCD Pain Phenotype Transformation

- Acute (chronic) vaso-occlusive only → Acute (chronic) vaso-occlusive + central and/or peripheral chronic neuropathic (neuroplasticity)
  - How often unknown
  - Mechanisms of phenotype transformation being studied
    - Summative ischemia on neurons
    - Genetic predisposition (different than 6 beta Hb Val→Glu)
    - Threshold effects
    - Timing

- Approaches to Rx (besides HU, L-glutamine, and transplant) unknown
  - Opioids being used but not studied
  - non-opioid chemical used but little studied
  - Other, including biobehavioral little used, little studied
Evolution to Chronic Pain in SCD?

Graph showing the evolution of pain severity over time (Age, Months) with different types of pain represented by markers:
- Vaso-occlusive pain (acute, intermittent, nociceptive)
- Pain from bone and tissue necrosis (chronic, nociceptive)
- Neuroplasticity induced by recurrent nociceptive input (chronic, neuropathic)
- Opioid-induced Hyperalgesia (acute or chronic, neuropathic)
Chronic SCD Pain–AAPT Definition--2017

- Diagnosis of SCD confirmed by laboratory testing, plus
  - Reports of ongoing pain present on most days over the past 6 months either in a single location or in multiple locations, and
  - One sign of pain sensitivity on palpation or with movement of the region of reported pain, decreased range of motion or weakness in the region of reported pain, or evidence of chronic disease complications (eg, skin ulcer, splenic infarct, or bone infarction) associated with the region of reported pain.
  - Three diagnostic modifications allowable
    - Chronic SCD pain without contributory disease complications
    - Chronic SCD pain with contributory disease complications
    - Chronic SCD pain with mixed pain types
      - Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative.
<table>
<thead>
<tr>
<th>Topic/Question</th>
<th>Evidence currently available</th>
<th>Evidence should be developed</th>
<th>Evidence may never be developed</th>
<th>Comments (How to develop, or why may never be developed)</th>
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| Efficacy of acute opioids to reduce acute SCD pain during a single VOC*--unselected patients | ✓                           | ✓                            |                                | • Emergency Department clear  
• Inpatient not clear  
• More RCT Inpatient trials of opioid administration strategies |
| Harms of acute opioids to reduce acute SCD pain during a single VOC* | ✓                           |                              |                                | • Emergency Department clear  
• Inpatient not clear  
• More RCT Inpatient trials of opioid administration strategies |
| Efficacy of acute opioids to reduce acute SCD pain among selected patients | ✓                           |                              |                                | Acute pain/unknown |
| Harms of acute opioids to reduce acute SCD pain among selected patients | ✓                           |                              |                                | Acute pain/unknown |
Discussion: What other types of studies might be easier to do than RCTs and do they help with understanding opioid prescribing for sickle cell disease?

– Improve the definitions of SCD pain phenotypes, tease out acute pain from chronic, nociceptive from neuropathic
  • Patient-reported Descriptor evidence
  • Quantitative Sensory Testing evidence
  • Functional Magnetic Resonance, Imaging evidence

– Conduct Mechanistic animal and human studies of opioids for these phenotypes
Highlights of 2011 NIH Portfolio: Interagency Pain Research Coordinating Committee

Topics

- Pain outcome assessments and measures 13%
- Health disparities in pain, pain management, and access to care 11%
- Genetics and genomics of nocioception and pain 7%
- Medical management of pain 7%
- Pharmacological mechanisms and treatment 7%
- Development and validation of animal models 9%
- Total 54%

- Total no. SCD pain grants < any other pain condition
  - Rare disease
  - relatively recent interest in this field
- Basic and translational research < other conditions
Gaps & Opportunities: Research areas needed or untapped

- Missing studies characterizing SCD pain phenotype(s) or diagnosis/case definitions
  - Ischemic noicioceptive
  - neurological
  - inflammatory
  - Biobehavioral
  - psychosocial

- Missing studies developing analgesics, device, and therapy delivery systems targeted at these mechanisms.
FDA-ASH Sickle Cell Disease Clinical Endpoints Workshop

October 17-18, 2018
Hilton Washington DC/Rockville Hotel & Executive Meeting Center, Rockville, MD
Conclusion of FDA/ASH Clinical Endpoints Workshop

**Challenges Developing Biomarkers for VOC**

- No validated biomarkers are currently available
- Existing clinical trial endpoints often do not distinguish between acute and chronic pain
- Pain scores may be subjective
- Opioid use may not be under completely under patient control
- Hospitalization metrics may be influenced by psychosocial factors
Biomarkers Useful for Trials: Guidance from the NIH/FDA

- The FDA/NIH Leadership Council identified harmonization of biomarker-related terms as a priority to improve communication and shared understanding of related terms among stakeholder groups (regulatory, scientific, business, and health care providers).

- An inter-agency biomarker working group, formed in 2015, developed an initial draft of a biomarker glossary of terms. The first release in 2016, called the BEST (Biomarkers, EndpointS, and other Tools) resource, is located on the NLM website (http://www.ncbi.nlm.nih.gov/books/NBK326791/):
  - Intended as a living document that can be updated and enhanced
Possible Clinical Endpoints for VOC

- Hospitalizations
  - Number per unit time
  - Time to first hospitalization
  - Time to next hospitalization
  - Duration of hospitalization or readiness for discharge

- Pain Diaries
  - Number of days pain is reported
  - Pain severity

- Pain scores
  - FACES (pediatric)
  - QoL questionnaires

- Opioid use
  - Inpatient
  - Outpatient
Possible Lab Biomarkers for VOC

- Markers of inflammation
  - CRP
  - Substance P

- Markers of hemolysis
  - Microparticles
  - Cell-free DNA
  - Plasma free heme
  - arginine

- Markers of vascular damage/adhesion
  - Nitric oxide
  - Endothelial progenitor cells
  - VCAM
  - VEGF

- Rheology
  - Viscosity
  - Dense cells
  - Deformability
  - Migration time through a laminin lined microvascular network
Discussion Question 1: Could the draft framework be used to develop a CPG for prescribing opioid for acute pain for your medical indication? What improvements would you suggest?

• The framework applies best to acute SCD pain WITHOUT Chronic pain

• The framework is less applicable when acute SCD pain occurs WITH complications (AAPT type 2) or WITH Chronic pain
  – Mid-term and long-term outcomes no longer purely from acute pain management
Discussion Question 2a: What evidence would be necessary to make the links in the framework or what additional information would bring existing clinical guidelines up to the standards indicated in the draft framework?

- Framework Step 1 is knowable, RCTs are feasible.
- Framework links 2-5 not completely knowable unless acute SCD pain were single event.
  - It is MULTIPLE Events
Discussion Question 2b: How might the evidence be generated and what tradeoffs might be necessary in conducting various types of studies (e.g., time, cost, practicality, resources)?

- Templates for single episode inpatient SCD pain management RCTs (Framework Step 1 evidence) are in the literature
Discussion Question 3: How would you conduct studies for conditions where RCTs might be impractical or where resources (e.g., patients) are scarce?

- Clinical trial networks agree to complex trial designs
  - to save person-months of study entry

- Nest randomized controlled trials in current longitudinal registry-like studies (U-01s at NHLBI, PCORI)
Discussion Question 4: How can the practicality, dissemination, and use of these CPGs be improved for the clinical setting or where clinical trials differ from real-world clinical practice, and if so, how might this be addressed?

• Difficult

• Many competing goals
  – Opioid safety
  – Patient satisfaction
  – Objective measurement of a subjective symptom
  – Adherence to federal, state, local laws
  – Avoiding misuse
  – Removing both patient stigma and physician stereotypes in order to enhance effectiveness of CPG-adherent care
Discussion Question 5: Are there prescribing nuances for opioids that should be captured in a clinical practice guideline for this medical indication?

Many nuances, described in previous slides