PAINWEEK®

Dulling the Scythe: New Approaches To The Management Of Sickle Cell Disease

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Disclosure

- Nothing to disclose

Learning Objectives

- Recall the pathophysiology of sickle cell disease and complications
- Review the most recent medication additions to the management of sickle cell disease
- Summarize the strategies for acute, chronic and acute-on-chronic pain management for the sickle cell patient

News You Can Use

- The opioid epidemic has forced many health care providers to enact changes in their policies
- This is an example of changing IV push hydromorphone into an IV infusion
- Providing this dose over a period of time had unintended effects for a patient

https://www.npr.org/sections/health-shots/2020/01/02/782654754/effort-to-control-opioids-in-an-er-leaves-some-sickle-cell-patients-in-pain accessed 1.27.2020

Effort To Control Opioids In An ER Leaves Some Sickle Cell Patients In Pain

January 2, 2020 · 4:10 PM ET

Heard on All Things Considered

Striking a balance

St. Mary's staffers explain that they're trying to strike a balance with their new treatment protocol between adequate pain treatment and the risk that opioid use can lead to drug dependence.

Hardy tries to manage these crises on her own. She'll take a hot bath or apply heating pads to try to increase her blood flow. Hardy also has a variety of pain medications she can take at home.

When she has exhausted all those options, she needs more medical help. Hardy would prefer to go to a specialized clinic for sickle cell patients, but the closest is almost two hours away and she doesn't have a car.

So, Hardy often goes to the emergency room at nearby St. Mary's Hospital for relief. Until recently, the doctors there would give her injections of the opioid hydromorphone, which she says would stop her pain.

Then, some months ago, the emergency room changed its process: "Now they will actually put that shot in a bag which is full of fluids, so it's like you're getting small drips of pain medicine," Hardy says. "It's like torture."

History of sickle cell disease	
1910	James Herrick notes "peculiar, elongated sickle-shaped erythrocytes" in a patient with anemia
1970	Sickle cell anemia becomes the first human disease to be explained at the level of a single nucleotide mutation: Using recombinant DNA technology techniques, scientists find that the nucleotide change in the DNA for sickle hemoglobin results from an A to T substitution
1983	The Prophylactic Penicillin Study (PROPS) finds that treatment of well sickle cell patients with penicillin could prevent death related to serious infections
1995	The Multicenter Study of Hydroxyurea proves the usefulness of hydroxyurea in preventing complications in patients with sickle cell disease
2001	Gene therapy successfully cures a sickle-cell mouse
2005	Genetic methods are developed to predict complications of sickle cell disease
2007	Techniques are developed in sickle-cell mice to convert normal cells into stem cells to be used for gene therapy and transplant

https://www.hematology.org/About/History/50-Years/1533.aspx accessed 1.24.2020

Demographics

- Sickle cell disease affects approximately 100,000 Americans
  - 1:365 African-American births
  - 1:16,300 Hispanic-American births
  - 1:13 African-Americans are born with sickle cell trait
    - NOT pathologic
- Mortality decreased by 42% from 1999 to 2002
  - Pneumococcal vaccinations were introduced in 2000
- Current mortality during the first three years of life: 1%

https://www.cdc.gov/ncbddd/sicklecell/data.html accessed 1.17.2020

Demographics, cont.

- Economic impact
  - –From 1989 through 1993, an average of 75,000 hospitalizations due to sickle cell disease occurred in the United States, costing approximately $475 million
  - –During 2005, medical expenditures for children with sickle cell disease averaged $11,702 for each child with Medicaid coverage and $14,772 for children with employer-sponsored insurance
    - •About 40% of both groups had at least one hospital stay

https://www.cdc.gov/ncbddd/sicklecell/data.html accessed 1.17.2020

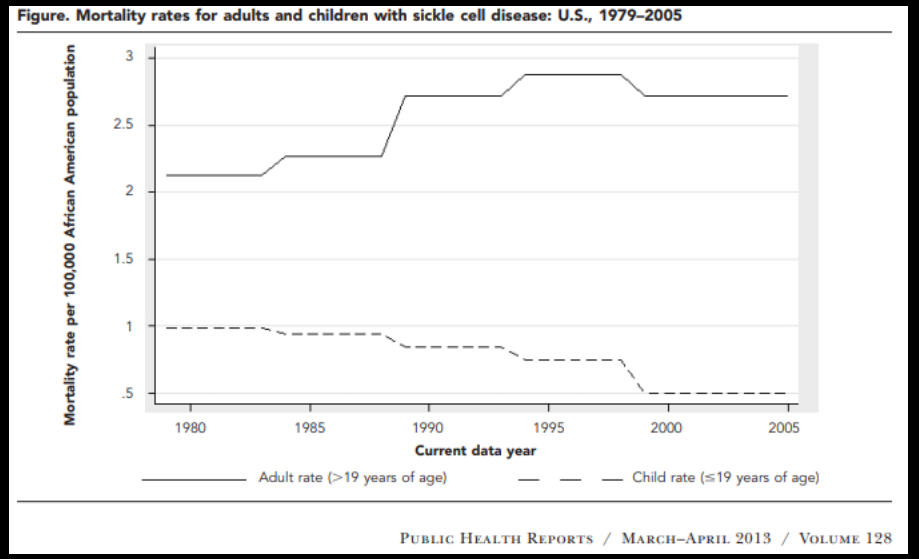
Demographics - Survival

1970

- –Average life expectancy, less than 20 years

1979-2005

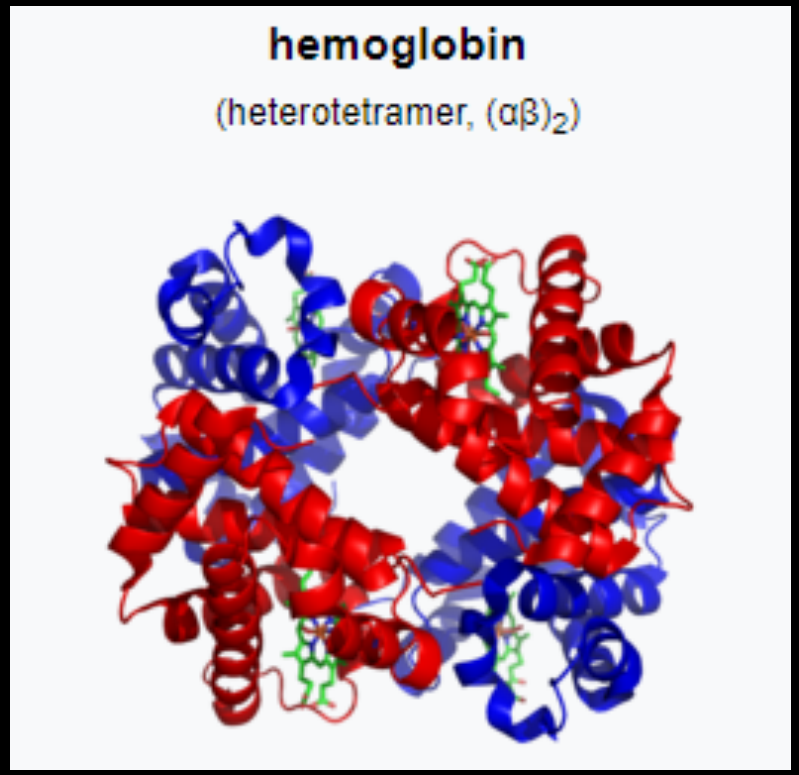
- –Average life expectancy for males, 38
- –Average life expectancy for females, 42



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3560868/pdf/phr128000110.pdf accessed 1.17.2020

Hemoglobin Review

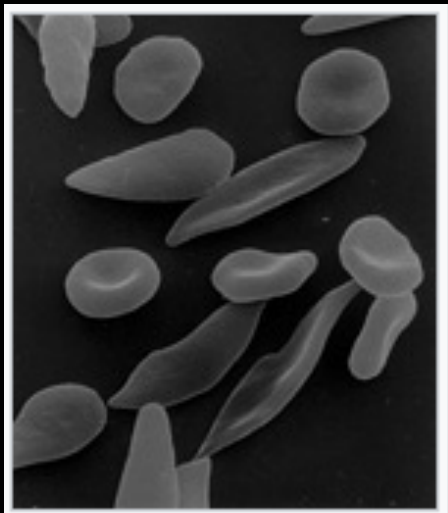
- Adult hemoglobin
  - –A ($\alpha_2\beta_2$)
  - –A2 ($\alpha_2\delta_2$)
  - –F ($\alpha_2\gamma_2$)
- Pathologic hemoglobin
  - –Thalassemia
    - •α and β
  - –C ($\alpha_2\beta^C{}_2$)
  - –S ($\alpha_2\beta^S{}_2$)
    - •Traditional sickle cell disease



http://en.wikipedia.org/wiki/Sickle-cell_disease accessed 1.17.2020

Sickle Cell Diagnostics

- Diagnostic testing with hemoglobin electrophoresis
- Percentages of Hemoglobin (Hb) (A, A_2, F, S)
  - –HbS > 90%; HbA_2 < 3.5%; HbA = zero
- Average Hb 6-8 g/dL in sickle cell disease
  - –High reticulocyte count
- Evidence of splenic impact
  - –Howell-Jolley bodies and Target cells



Scanning electron micrograph showing a mixture of red blood cells, some with round normal morphology, some with mild sickling showing elongation and bending

http://en.wikipedia.org/wiki/Sickle-cell_disease accessed 1.17.2020

Sickle Cell Variants

- Hemoglobin SC pathology
  - –Second most common form of sickle cell disease
  - –Primary difference is the decreased incidence of severe anemia
  - –Mild splenomegaly and anemia
- Sickle cell trait
  - –Three million in the US
    - •Fifty times more prevalent than those with sickle cell disease
  - –No objective evidence in terms of anemia

Complications

- Acute chest syndrome
- Stroke
- Pulmonary hypertension
- Hepatic and splenic sequestration
- Infections

- Acute and chronic pain

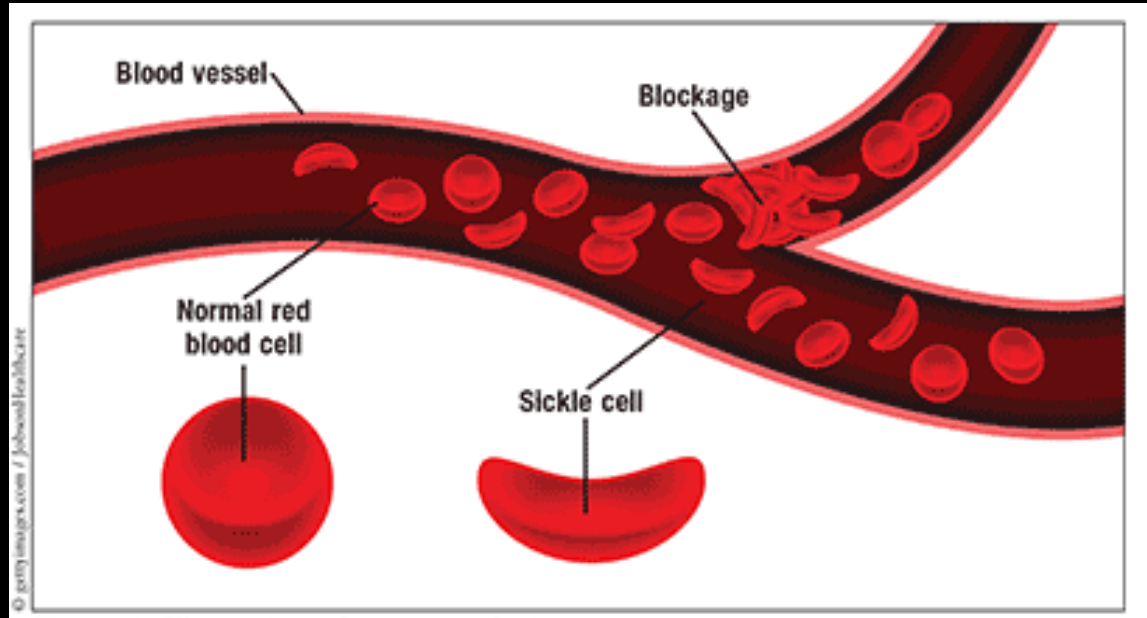


Figure 1. Illustration of a vaso-occlusive event.

https://www.uspharmacist.com/article/sickle-cell-disease-pain-management accessed 1.24.2020

Vaso-occlusive Crisis (VOC)

- The most common clinical manifestation
  - –Obstruction of the microcirculation
    - •Marrow producing bones
    - •Viscera
- Frequency is highly variable
  - –Annual occurrences per patient are generally consistent
- Triggers for a VOC include
  - –Hypoxemia
  - –Dehydration
  - –Temperature changes

Adapted from https://www.yalemedicine.com/understanding-sickle-cell-disease/how-sickle-cell-disease-affects-the-body/ accessed 1.24.20

https://emedicine.medscape.com/article/205926-print accessed 1.24.2020

Phases of Vaso-occlusive Crisis

1. Prodromal phase
   - Fatigue, weakness, yellowing of eyes, paresthesia
2. Initial evolving infarctive phase
   - Pain increases, changes in behavior, anorexia
3. Post-infarctive phase
   - Persistent severe pain
   - Notable changes in laboratory values
4. Resolving phase (post-crisis)
   - Gradually remits over a period of one to two days
   - Behaviors, pain and lab values return to baseline

https://www.jpsmjournal.com/article/S0885-3924(05)00050-3/pdf accessed 1.24.2020

Acute Into Chronic Pain

- Chronic pain develops irrespective of vaso-occlusive crisis in 29.3% of adults
  - –40% of children (8-18 years) have chronic pain with 35% reporting daily pain
- Chronic pain described is both neuropathic and nociceptive in quality
- Diagnostic sensory testing indicate increases in sensitivity to thermal and mechanical stimuli
- fMRI changes and windup suggest the pathology to be both peripheral and centrally mediated in origin

Brandow AM, et. al. Sickle cell disease: a natural model of acute and chronic pain. Pain 158(S1): S79-84 2017.

Novel Approaches To Sickle Cell Prevention

FDA approved agents added since 2017

- L-glutamine
- Hydroxyurea
- Voxelotor
- Crizanlizumab-tmca

https://www.health.harvard.edu/blog/disposing-expired-unused-medications-gets-whole-lot-easier-safer-weekend-20170427116 83 accessed 3.5.2020

L-glutamine

- Amino acid thought to prevent oxidative damage in red blood cells though increased availability of glutathione
- Oral powder for administration
  - –Dosing is based on patient weight

Weight in kilograms	Weight in pounds	Per dose in grams	Per day in grams	Packets per dose	Packets per day
less than 30	less than 66	5	10	1	2
30 to 65	66 to 143	10	20	2	4
greater than 65	greater than 143	15	30	3	6

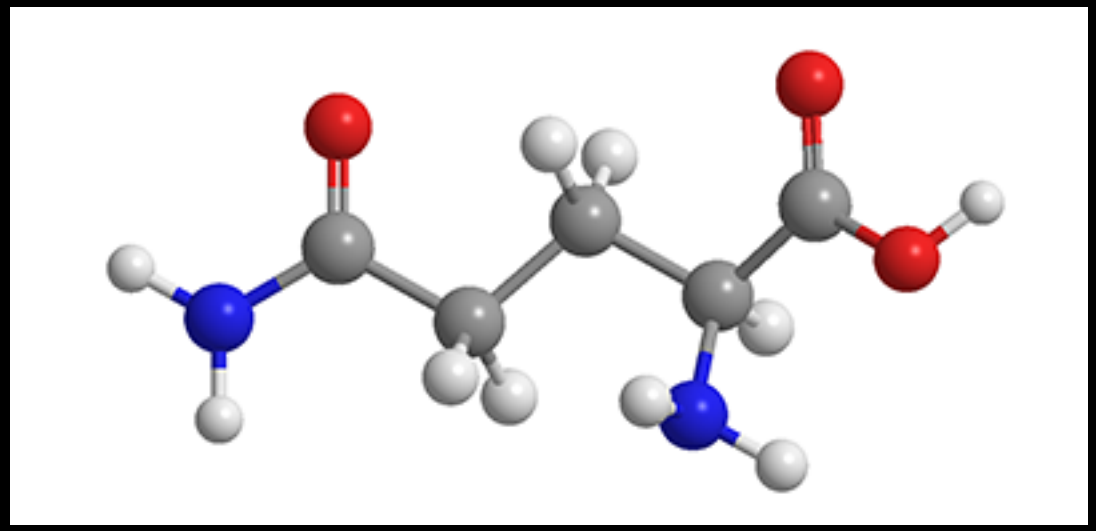
- May be administered with 8 oz. of oral fluids or soft food

https://www.rxlist.com/endari-drug.htm#description accessed 1.1.2020

L-glutamine cont.

- Formulation is not bioequivalent to other glutamine supplements
  - –Lack of standardization of dose with supplements

❖Average cumulative vaso-occlusive crisis count was reduced by 25% over a 48 week period in patients with sickle cell +/- β–thalassemia



https://www.acs.org/content/acs/en/molecule-of-the-week/archive/g/l-glutamine.html accessed 1.1.2020

* A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle βo – thalassemia. NCT01179217

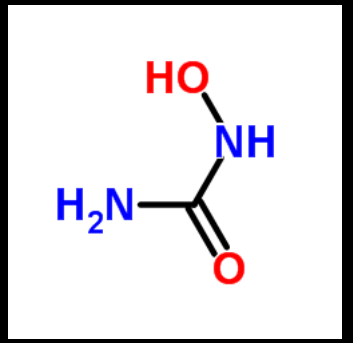
Hydroxyurea

- Antimetabolite indicated to reduce frequency of vaso-occlusive crises and need of transfusions in pediatric patients 2 years and older
- Initial dosing 20 mg/kg based on weight
  - –NOT the initial 15 mg/kg dosing of other hydroxyurea products
  - –Maximum dosing is 35 mg/kg or until myelosuppression occurs
  - –Myelosuppression defined as
    - Neutrophils < 2000/ mm^3
    - Platelets < 80,000/ mm^3
    - Hemoglobin < 4.5 g/dL
    - Reticulocytes < 80,000 if Hgb < 9 g/dL

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208843s000lbl.pdf accessed 1.1.2020

Hydroxyurea cont.

- Clinical response may take up to six months of continuous treatment
- ❖ Among patients naïve to hydroxyurea, treatment over 12 months decreased the number of VOCs, ACS, hospitalizations and number of blood transfusions



ACS = acute chest syndrome
VOC = vaso-occlusive crisis

* https://clinicaltrials.gov/ct2/show/NCT02516579 accessed 1.1.2020

https://www.goldbio.com/product/13238/hydroxyurea accessed 1.1.2020

Voxelotor

- Polymerization inhibitor to increase the affinity of oxygen to Hemoglobin S
- Indicated for patients 12 years and older
- Initial dosing is 1500 mg by mouth daily
  - –Patients with hepatic impairment (Child Pugh C) 1000 mg daily

Table 1: OXBRYTA Recommended Dosage for Concomitant Medications

Concomitant Medication	Recommended OXBRYTA Dosage
Strong CYP3A4 inhibitors or fluconazole	1,000 mg once daily
Strong or moderate CYP3A4 inducers	2,500 mg once daily

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213137s000lbl.pdf accessed 1.2.2020

Voxelotor cont.

HOPE 3 trial

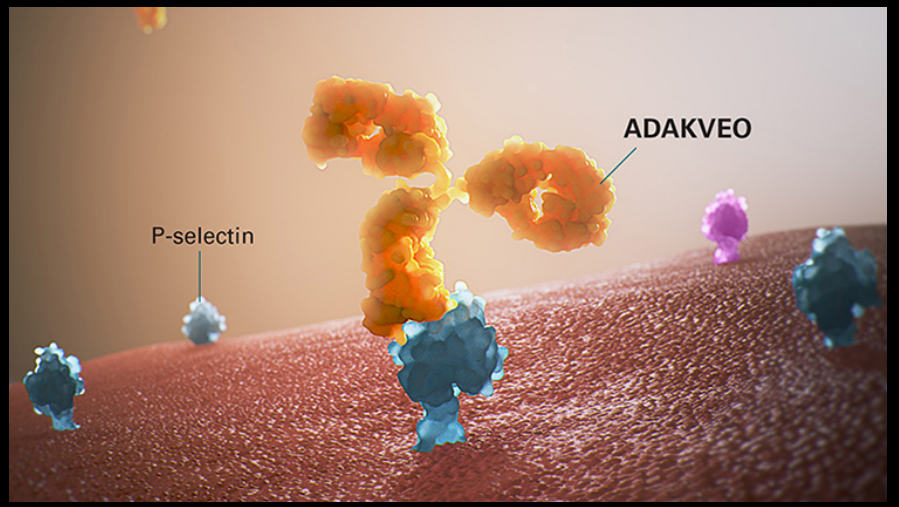
- Included 274 patients with sickle cell +/- β^0-thalassemia received either 1500 mg, 750 mg or placebo daily
  - –66% of patients were on hydroxyurea at baseline
- At 24 weeks the 1500 mg group had a 51% hemoglobin response (increase) compared to 7% for placebo
- No statistical impact on vaso-occlusive crisis nor adverse drug events related to sickle cell disease pathology

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med 2019;381:509-19.

Crizanlizumab-tmca

- Humanized $IgG_{2\kappa}$ monoclonal antibody which binds to P-Selectin and blocks interactions with the P-Selectin ligand
  - –This prevents the activated endothelium and platelets from interaction and decrease frequency of vaso-occlusive crisis
- Indicated for patients 16 years and older
- Dosing is 5 mg/kg IV over 30 minutes
  1. Initial dosing
  2. Two weeks later
  3. Every four weeks thereafter

https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/adakveo.pdf accessed 1.27.2020



https://www.hcp.novartis.com/products/adakveo/sickle-cell-disease/mechanism-of-action/ accessed 1.27.2020

Crizanlizumab-tmca, cont.

- Patients with Hemoglobin S, C or β-thalassemia between 16-65 and with 2-10 VOC in the past 12 months were eligible
- Crizanlizumab was dosed 5 mg/kg, 2.5 mg/kg or placebo for 52 weeks
- Primary endpoint: number of VOCs in 12 months

Primary endpoint results

Group	Median VOC over 12 months	Statistical analysis compared to placebo
High dose (5 mg/kg)	1.63	45.3% lower; P = 0.01
Low dose (2.5 mg/kg)	2.01	32.6% lower; P = 0.18
Placebo	2.98	-

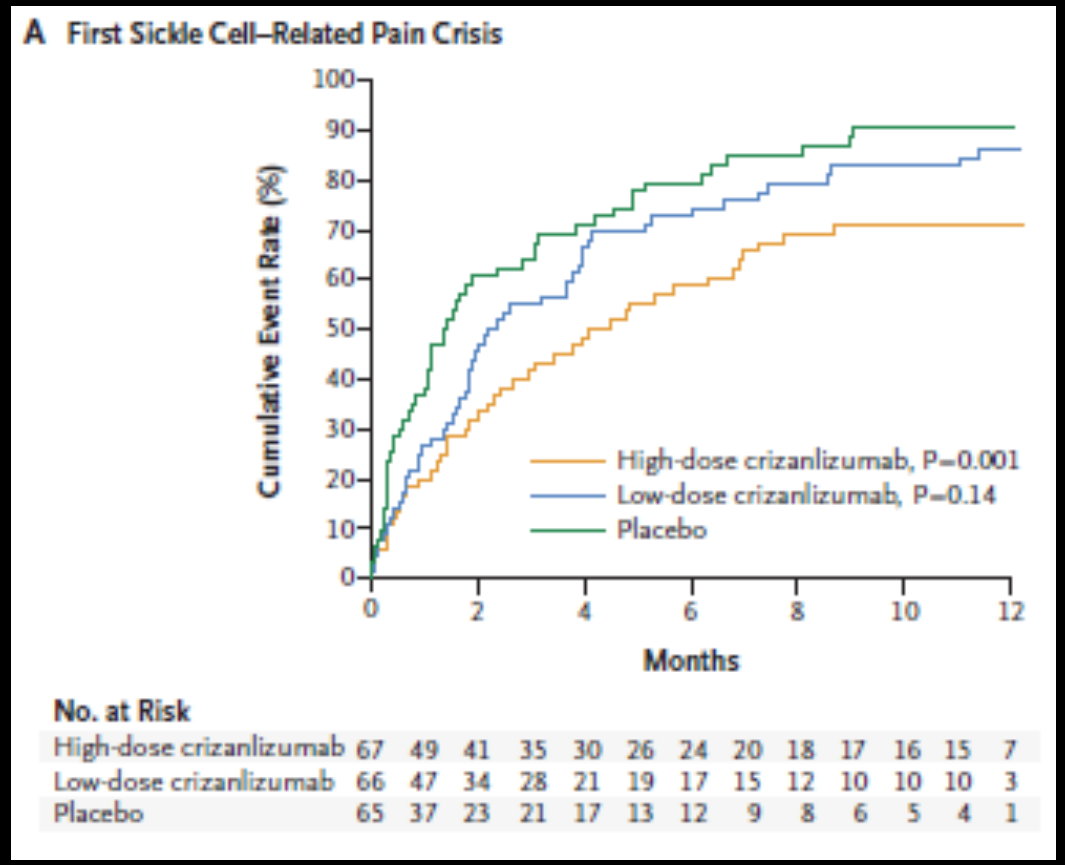
Ataga KI, et.al. Crizanlizumab for the prevention of pain crises in sickle cell disease NEJM 376: 429-39 2017
VOC = vaso-occlusive crisis

Crizanlizumab-tmca, cont.

Secondary results

- –No difference in hospitalizations
- –Time to first vaso-occlusive crisis
  - •4.07 months (5 mg/kg) v. 1.38 months (placebo)
    - –P = 0.001

- Safety
  - –Increase in pyrexia and influenza in the treatment groups



Ataga KI, et.al. Crizanlizumab for the prevention of pain crises in sickle cell disease NEJM 376: 429-39 2017

The price for Progress

Two New Drugs Help Relieve Sickle-Cell Disease. But Who Will Pay?

Adakveo and Oxbryta could be revolutionary treatments, but each costs about $100,000 per year and must be taken for life.

Adakveo, made by Novartis, can prevent episodes of nearly unbearable pain that occur when malformed blood cells get stuck in blood vessels. Approved only for patients aged 16 and over, it is delivered as an infusion once a month.

Oxbryta, made by Global Blood Therapeutics, can prevent severe anemia from the disease that can lead to permanent damage to the brain and other organs. A daily pill, the drug is approved for patients ages 12 and older.

Each treatment is priced at around $100,000 a year and must be taken for life. While it is not uncommon for a drug treating a rare disease to carry such a high price, there are 100,000 people with sickle-cell disease in the United States, and millions more around the world.

Those prices are about double the median family income in the United States, "highlighting a growing dysfunction in the pharmaceutical market," said Ameet Sarpatwari, assistant director of the Program on Regulation, Therapeutics and Law at Brigham and Women's Hospital in Boston.

https://www.nytimes.com/2019/12/07/health/sickle-cell-adakveo-oxbryta.html accessed 1.27.2020

Breakthrough Therapy Designation Granted for Sickle Cell Disease Treatment

Patients with SCD face a high economic burden, with annual costs of more than $30,000 for adults with the disease, according to Novartis. SCD can lead to VOCs, which are painful complications caused by clusters of cells that block or reduce blood flow.

https://www.pharmacytimes.com/news/breakthrough-therapy-designation-granted-for-sickle-cell-disease-treatment accessed 1.27.2020

Looking Toward the Future

> >The following agents are not FDA approved for the management of sickle cell disease< <

- Ticagrelor
- N-acetyl-cysteine
- IVIG
- Propranolol
- IV magnesium

****NONE of the following are FDA approved for use to treat patients****

- Rivipansel - Pan-selectin antagonist
- Sevuparin - P-selectin antagonist, derived from heparin
- Omega-3 fatty acids
- α-lipoic acid

Matte A., Zorzi F., Mazzi F., Federti E., Olivieri O., De Franceschi L. New therapeutic options for the treatment of sickle cell disease. Mediterr J Hematol Infect Dis 2019, 11(1): e2019002
Kapoor S, et. al. Advances in the Treatment of Sickle Cell Disease Mayo Clin Proc. 2018;93(12):1810-1824

Management of Sickle Cell

- Prevention
- Acute pain management
- Chronic pain management
- Guidelines

Adapted from https://images.app.goo.gl/2qPw493ZgfoRQEss5 accessed 1.30.2020

Vaso-occlusive Crisis (VOC) Prevention

- Minimizing triggers for VOC
  - –Increase temperature or minimize environmental exposures
  - –Staying hydrated
  - –Not overexerting
  - –Avoiding respiratory exposure
- Hydroxyurea
- L-Glutamine

Transfusions?

https://www.cornerstonesmiles.com/blog/prevention-vs-treatment-of-oral-health/ accessed 1.28.2020

Vaso-occlusive pain management in sickle cell disease UpToDate accessed 1.28.2020

Acute Pain Management- Home

- Mild pain
  - –NSAIDs
  - –Acetaminophen
- Moderate to severe pain
  - –Opioids
    - Immediate release
    - Extended release
- Cannabinoids

Vaso-occlusive pain management in sickle cell disease UpToDate accessed 1.28.2020

- Non-pharmacologic
  - –Hydration
  - –Sleep architecture
- Having a plan when home therapy is ineffective or for more serious symptoms
  - Avoid
    - Ice or cold therapy
    - Opioids that contain acetaminophen
    - Codeine

Acute Pain Management- Health Care Setting

Emergency Department or Day Hospital

- Prompt IV analgesia
  - –Initial dose of IV morphine 0.1-0.15 mg/kg, max 10 mg
  - –Initial dose of IV hydromorphone 0.02-0.05 mg/kg, max 1.5 mg
  - –Use previously effective doses for subsequent encounters

- Intranasal fentanyl may also be trialed for children >3 kg and <10 kg using 1.5 mcg/kg, max 100 mcg
  - –Fentanyl is also preferred for those with hepatic or renal dysfunction

Vaso-occlusive pain management in sickle cell disease UpToDate accessed 1.28.2020

Acute Pain Management- Health Care Setting, cont.

- Avoiding ineffective therapies
  - Placebo
  - Sedatives and anxiolytics for pain management
  - Ketorolac and other NSAIDs
    - Increased odds of developing acute kidney injury by 63%
      - Odds ratio 1.63, 95% CI 1.08-2.47
  - Oxygen without objective evidence of hypoxemia
  - Transfusions for [patient baseline] anemia without other complications
    - Stroke
    - Acute chest syndrome

Vaso-occlusive pain management in sickle cell disease UpToDate accessed 1.28.2020

Opioids in Acute Vaso-occlusive Crisis

Table 2. Starting Doses for Opioid Analgesics in Opioid-Naive Adults and Children >50 kg Body Weight With Moderate-to-Severe Pain

Medication	Oral	Parenteral
Short-Acting Opioid Agonists		
Morphine	10-30 mg q3-4h	5-10 mg q2-4h
Hydromorphone (Dilaudid)	7.5 mg q3-4h	1.5 mg q3-4h
Oxymorphone (Numorphan)	NA	1-1.5 mg q6h or 0.5 mg IV and cautiously titrate upward
Oxycodone	10 mg q4-6h	NA
Combination Opioid/NSAID Preparations		
Hydrocodone	10 mg q3-4h	NA

NA: not applicable; NSAID: nonsteroidal anti-inflammatory drug.
Note: 1. Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics. 2. Because it is not possible to determine the appropriate starting dose of controlled-release opioids without knowing the patient's opioid requirements as determined by immediate-release preparation, usual starting doses are not listed for long-acting medications. 3. Although published tables vary in the suggested doses for moderate-to-severe pain episodes, titration to clinical response is the criterion that must be applied to each patient. Source: References 1-3, 13.

Table 3. Starting Doses for Opioid Analgesics in -Naive Adults and Children <50 kg Body Weight With Moderate-to-Severe Pain

Medication	Oral	Parenteral
Short-Acting Opioid Agonists		
Morphine	0.3 mg/kg q3-4 h	0.1-0.15 mg/kg q2-4h
Hydromorphone	0.06-0.08 mg/kg q3-4h	0.015-0.020 mg/kg q3-4h
Oxycodone	0.15-0.20 mg/kg q3-4h	NA

NA: not applicable; NSAID: nonsteroidal anti-inflammatory drug.
Note: 1. Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics. 2. Because it is not possible to determine the appropriate starting dose of controlled-release opioids without knowing the patient's opioid requirements as determined by immediate-release preparation, usual starting doses are not listed for long-acting medications. 3. Although published tables vary in the suggested doses for moderate-to-severe pain episodes, titration to clinical response is the criterion that must be applied to each patient.
Source: References 1-3, 13.

https://www.uspharmacist.com/article/sickle-cell-disease-pain-management
accessed 1.29.2020

Patient Controlled Analgesia

- Multiple parenteral opioids to chose from
- Medication delivery settings generally include
  - –Strength and frequency of patient administered dose
  - –Additional clinician bolus dose and frequency
  - –Continuous (basal) infusion
  - –Lock out settings
    - •Frequency of doses or overall amount per time frame
- Gives the patient more control over their analgesia
- Increased patient satisfaction, still have safety limits in place

Caution should be exercised with basal infusions

Chronic Sickle Cell Pain Management

- Quality of pain can be nociceptive, neuropathic or both
- The quality of the pain determines how to deal with the pain pharmacologically
  - –Nociceptive versus neuropathic
- This may also be part of background pain during an vaso-occlusive crisis
  - –The quality of the acute on chronic pain may differ
    - ✓Acute nociceptive pain with background neuropathic pain

Chronic Sickle Cell Pain Management, cont.

Nociceptive pain

- Scheduled NSAIDs
- Scheduled opioids
  - –Immediate release around the clock, initially
  - –Extended release around the clock
  - –*Have breakthrough available for flares*

Neuropathic pain

- Anticonvulsants
  - –Not all are FDA approved for neuropathic pain
- Antidepressants
  - –SNRIs
  - ❑TCAs
  - ❑SSRIs

❑ Not FDA approved for pain management

Acute on Chronic Pain Management

- Continue current chronic pain management regimen
- Have protocols in place regarding evaluation and management of acute pain
  - –Education on when patients should contact their medical providers
  - –Opioid agreements with clear expectations of when and where to seek acute pain management
  - –Protocols from local day hospital or emergency care providers
- Manage nociceptive and neuropathic pain with appropriate pharmacology

What do experts have to say?

- Many of these are based on consensus statements or expert opinions
- The evidence based recommendations will be discussed

Evidence-Based Management of Sickle Cell Disease

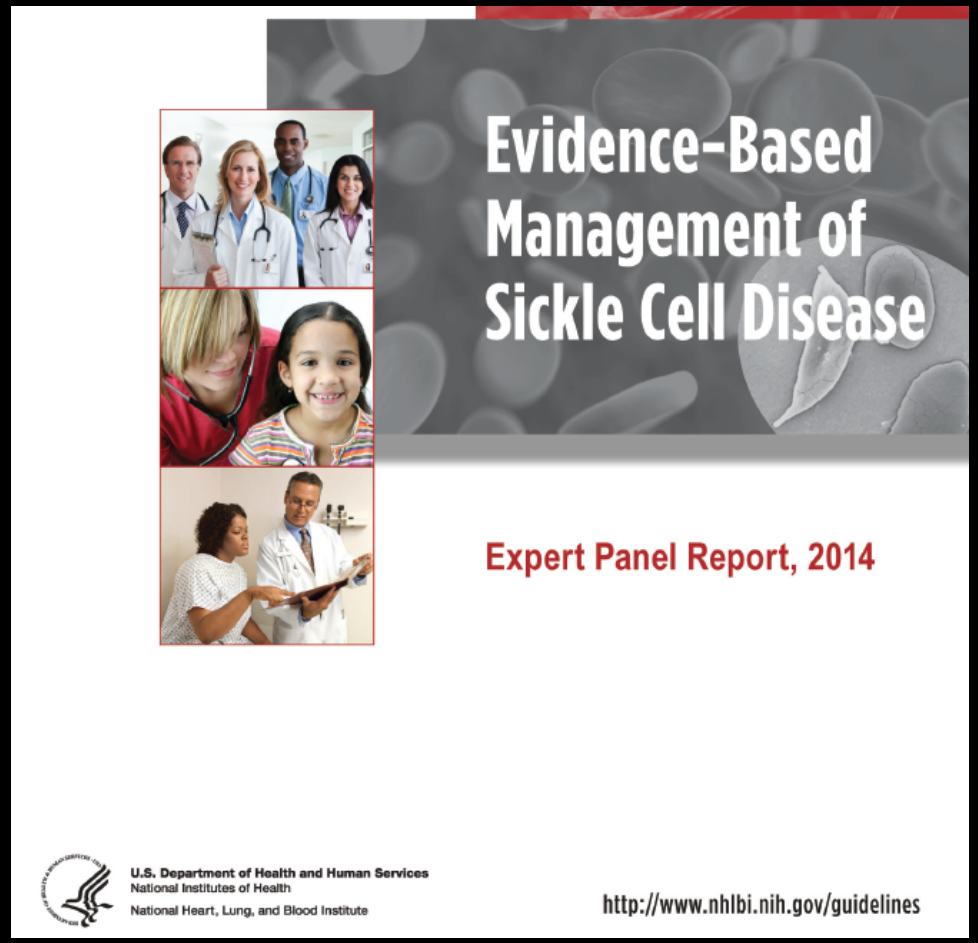
Expert Panel Report, 2014

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf accessed 1.29.2020

What Do Experts Have To Say?



- Many of these are based on consensus statements or expert opinions
- The evidence based recommendations will be discussed

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf accessed 1.29.2020

NHLBI Recommendations in VOC

1. In adults and children with SCD and a VOC associated with mild to moderate pain who report relief with NSAIDS in the absence of contraindications to the use of NSAIDS, continue treatment with NSAIDS. (***Moderate Recommendation, Low-Quality Evidence)***
2. In adults and children with SCD and a VOC associated with severe pain, rapidly initiate treatment with parenteral opioids. (***Strong Recommendation, High-Quality Evidence***)

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf accessed 1.29.2020

SCD = Sickle Cell Disease
VOC = Vaso-occlusive crisis
NSAIDs = non-steroidal anti-inflammatory drugs

NHLBI Recommendations in VOC, cont.

3. Initiate around-the-clock opioid administration by patient-controlled analgesia or frequently scheduled doses versus “as requested” administration. (***Moderate Recommendation, Low-Quality Evidence)***
4. To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC, encourage use of incentive spirometry while awake. ***(Strong Recommendation, Moderate-Quality Evidence)***
5. In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion. (***Moderate Recommendation, Low-Quality Evidence***)

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf accessed 1.29.2020

SCD = Sickle Cell Disease
VOC = Vaso-occlusive crisis

CDC Prescribing guidelines

- Initially published in 2016
  - ≥ 90 morphine milligram equivalents
- Some of these recommendations are being misapplied by state boards, insurance companies, etc.
  - Examples of misapplication include applying the CDC opioid prescribing guideline to patients in active cancer treatment, patients experiencing acute sickle cell crises, or patients experiencing post-surgical pain

https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html accessed 2.3.2020

CDC Prescribing Guidelines, cont.

- **Misapplication of recommendations to populations outside of the Guideline's scope.** The Guideline is intended for primary care clinicians treating chronic pain for patients 18 and older. Examples of misapplication include applying the Guideline to patients in active cancer treatment, patients experiencing acute sickle cell crises, or patients experiencing post-surgical pain.
- **Misapplication of the Guideline's dosage recommendation that results in hard limits or "cutting off" opioids.** The Guideline states, "*When opioids are started*, clinicians should prescribe the lowest effective dosage. Clinicians should… avoid *increasing* dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day." The recommendation statement does not suggest discontinuation of opioids already prescribed at higher dosages.
- **The Guideline does not support abrupt tapering or sudden discontinuation of opioids**. These practices can result in severe opioid withdrawal symptoms including pain and psychological distress, and some patients might seek other sources of opioids. In addition, policies that mandate hard limits conflict with the Guideline's emphasis on individualized assessment of the benefits and risks of opioids given the specific circumstances and unique needs of each patient.
- **Misapplication of the Guideline's dosage recommendation to patients receiving or starting medication-assisted treatment for opioid use disorder.** The Guideline's recommendation about dosage applies to use of opioids in the management of chronic pain, not to the use of medication-assisted treatment for opioid use disorder. The Guideline strongly recommends offering medication-assisted treatment for patients with opioid use disorder.

https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html accessed 2.3.2020

NHLBI recommendations in Chronic Pain

- Encourage people to use deep tissue/deep pressure massage therapy, muscle relaxation therapy, and self-hypnosis as indicated

(Weak Recommendation, Low-Quality Evidence)

In general, the quality of the available evidence was very low, so the expert panel determined that higher quality evidence with better precision should be derived from studies that evaluated chronic pain management in other settings. Such a body of evidence is larger and includes a wider scope of interventions and comparisons, which could lead to more useful recommendations for practitioners caring for people with SCD who have chronic pain. The panel and the methodology team appraised the quality of the guidelines for the management of chronic pain published by the American Pain Society in collaboration with the American Academy of Pain Medicine.[24] The quality of the guidelines was deemed acceptable, so the panel adapted selected recommendations applicable to people with SCD as shown below in the "Recommendations" section, and these are labeled accordingly.

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf accessed 1.29.2020

Chronic pain APS*-AAPM

1. Patient selection and risk stratification

1.1 Prior to initiating COT, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction (strong recommendation, low-quality evidence).

1.2 Clinicians may consider a trial of COT as an option if CNCP is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).

1.3 A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented prior to and on an ongoing basis during COT (strong recommendation, low-quality evidence).

2. Informed consent and opioid management plans

2.1 When starting COT, informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT (strong recommendation, low-quality evidence).

2.2 Clinicians may consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education (weak recommendation, low-quality evidence).

3. Initiation and titration of COT

3.1 Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate (strong recommendation, low-quality evidence).

3.2 Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms (strong recommendation, low-quality evidence). There is insufficient evidence to recommend short-acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.

Cho R, et. al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain *Pain*. 2009 February ; 10(2): 113–130. doi:10.1016/j.jpain.2008.10.008

COT= chronic opioid therapy
CNCP = chronic non-cancer pain

Chronic Pain APS*-AAPM, cont.

4. Methadone

4.1 Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously, by clinicians familiar with its use and risks (strong recommendation, moderate quality evidence).

5. Monitoring

5.1 Clinicians should reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress towards achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies (strong recommendation, low-quality evidence).

5.2 In patients on COT who are at high risk or who have engaged in aberrant drug related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care (strong recommendation, low-quality evidence).

5.3 In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care (weak recommendation, low-quality evidence).

6. High-risk patients

6.1 Clinicians may consider COT for patients with CNCP and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist (strong recommendation, low-quality evidence).

6.2 Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of COT or need for restructuring of therapy, referral for assistance in management, or discontinuation of COT (strong recommendation, low-quality evidence).

COT= chronic opioid therapy
CNCP = chronic non-cancer pain

Cho R, et. al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain *Pain*. 2009 February ; 10(2): 113–130. doi:10.1016/j.jpain.2008.10.008

Chronic Pain APS*-AAPM, cont.

7. Dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy

7.1 When repeated dose escalations occur in patients on COT, clinicians should evaluate potential causes and re-assess benefits relative to harms (strong recommendation, low-quality evidence).

7.2 In patients who require relatively high doses of COT, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits (strong recommendation, low-quality evidence).

7.3 Clinicians should consider opioid rotation when patients on COT experience intolerable adverse effects or inadequate benefit despite dose increases (weak recommendation, low-quality evidence).

7.4 Clinicians should taper or wean patients off of COT who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress towards meeting therapeutic goals, or experience intolerable adverse effects (strong recommendation, low-quality evidence).

8. Opioid-related adverse effects

8.1 Clinicians should anticipate, identify, and treat common opioid-associated adverse effects (strong recommendation, moderate-quality evidence).

9. Use of psychotherapeutic co-interventions

9.1 As CNCP is often a complex biopsychosocial condition, clinicians who prescribe COT should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies (strong recommendation, moderate-quality evidence).

10. Driving and work safety

10.1 Clinicians should counsel patients on COT about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment (strong recommendation, low-quality evidence).

Cho R, et. al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain *Pain*. 2009 February ; 10(2): 113–130. doi:10.1016/j.jpain.2008.10.008

COT= chronic opioid therapy
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Chronic Pain APS*-AAPM, cont.

11. Identifying a medical home and when to obtain consultation

11.1 Patients on COT should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe COT, but should coordinate consultation and communication among all clinicians involved in the patient's care (strong recommendation, low-quality evidence).

11.2 Clinicians should pursue consultation, including interdisciplinary pain management, when patients with CNCP may benefit from additional skills or resources that they cannot provide (strong recommendation, moderate-quality evidence).

12. Breakthrough pain

12.1 In patients on around-the-clock COT with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk (weak recommendation, low-quality evidence).

13. Opioids in pregnancy

13.1 Clinicians should counsel women of childbearing potential about the risks and benefits of COT during pregnancy and after delivery. Clinicians should encourage minimal or no use of COT during pregnancy, unless potential benefits outweigh risks. If COT is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn (strong recommendation, low-quality evidence).

14. Opioid policies

14.1 Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of COT for CNCP (strong recommendation, low-quality evidence).

Cho R, et. al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain *Pain*. 2009 February ; 10(2): 113–130. doi:10.1016/j.jpain.2008.10.008

COT= chronic opioid therapy
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Vaso-occlusive Crisis Patient Case

LL is a 28 M with sickle cell disease arriving at urgent care with severe pain in the back, bilateral arms and chest. He states he recently was in Denver, CO and these symptoms started shortly after coming home. He has tried to manage at home but the pain is now too intense, current pain 7/10, usual pain 3/10.

Medications at home: Morphine ER 60 mg q 12 hrs, oxycodone 10 mg IR q 4 hrs prn pain (averages 3 doses per day), meloxicam 15 mg daily, hydroxyurea 500 mg po q 12 hrs.

Vaso-occlusive Crisis Patient Case, cont.

Initial management included IV fluids and diagnostics including a chest X-ray, BMP and CBC w/ differential and initial treatments with IV opioids.

Any red flags on initial patient presentation?

Concern for acute chest syndrome

Follow up labs all WNL

- Hemoglobin = 6.5 mg/dL at baseline

Hospitalist accepts patient for inpatient admission: Rule Out Acute Chest Syndrome

Vaso-occlusive Crisis Patient Case, cont.

LL initially is restarted on home opioids but is actively vomiting, what other options are there?

Patient controlled analgesia [PCA]

What data would be used in your initial calculation for his PCA?

Vaso-occlusive Crisis Patient Case, cont.

1. Calculate total morphine milligram equivalent = 165 mg
   - –Oxycodone 10 mg q 4 hrs. [avg. 3 doses/day] = oxycodone 30 mg = morphine 45 mg
   - –Morphine 60 mg ER q 12 hrs. = 120 mg
2. Oral morphine equivalent daily dose = 165 mg = 55 mg IV morphine over 24 hours
   - –Approximate basal rate = 2 mg/hr [actual would be 2.3 mg/hr]
     - •Keep in mind incomplete cross tolerance with the oxycodone
3. Set the patient controlled morphine dosing initially as 1 mg every 6 minutes, clinician bolus of 5 mg every hour and 4-hour max of 40 mg

Vaso-occlusive Crisis Patient Case, cont.

Two days later after negative chest X-ray, hydration fluids and PCA morphine, LL's nausea has subsided and tolerated an oral fluids challenge. He still complains of pain over baseline and does not feel ready to go home. What are your next steps?

1. Restart hydroxyurea
2. Restart home analgesic regimen
3. Change PCA morphine to prn parenteral morphine (5-10 mg) every 4 hours as needed

One day post your interventions above, LL is back to baseline and ready for discharge and you agree clinically

Summary

- Sickle cell disease pain management is multifaceted and the approach to management must be the same
- Newer medications available assist patients by altering the pathophysiology and decrease acute vaso-occlusive crises
- It can be quite difficult to manage sickle cell patients in this age of the opioid epidemic however, it can be done safely