

American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain

Amanda M. Brandow,¹ C. Patrick Carroll,² Susan Creary,³ Ronisha Edwards-Elliott,⁴ Jeffrey Glassberg,⁵ Robert W. Hurley,^{6,7} Abdullah Kutlar,⁸ Mohamed Seisa,⁹ Jennifer Stinson,¹⁰ John J. Strouse,^{11,12} Fouza Yusuf,¹³ William Zempsky,¹⁴ and Eddy Lang¹⁵

¹Section of Hematology/Oncology/Bone Marrow Transplantation, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; ²Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD; ³Center for Innovation in Pediatric Practice, Division of Hematology, Oncology and Bone Marrow Transplant, Nationwide Children's Hospital, The Ohio State University School of Medicine, Columbus, OH; ⁴Department of Pediatrics, University of Illinois at Chicago, Chicago, IL; ⁵Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; ⁶Department of Anesthesiology and ⁷Department of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC; ⁸Center for Blood Disorders, Medical College of Georgia, Augusta University, Augusta, GA; ⁹Mayo Clinic Evidence-based Practice Research Program, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, MN; ¹⁰Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON, Canada; ¹¹Division of Hematology, Department of Medicine, and ¹²Division of Pediatric Hematology/Oncology, Department of Pediatrics, Duke University School of Medicine, Durham, NC; ¹³Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; ¹⁴Division of Pain and Palliative Medicine, Connecticut Children's Medical Center, Department of Pediatrics, University of Connecticut School of Medicine, Hartford, CT; and ¹⁵Department of Emergency Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Background: The management of acute and chronic pain for individuals living with sickle cell disease (SCD) is a clinical challenge. This reflects the paucity of clinical SCD pain research and limited understanding of the complex biological differences between acute and chronic pain. These issues collectively create barriers to effective, targeted interventions. Optimal pain management requires interdisciplinary care.

Objective: These evidence-based guidelines developed by the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in pain management decisions for children and adults with SCD.

Methods: ASH formed a multidisciplinary panel, including 2 patient representatives, that was thoroughly vetted to minimize bias from conflicts of interest. The Mayo Evidence-Based Practice Research Program supported the guideline development process, including updating or performing systematic reviews. Clinical questions and outcomes were prioritized according to importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used, including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel reached consensus on 18 recommendations specific to acute and chronic pain. The recommendations reflect a broad pain management approach, encompassing pharmacological and nonpharmacological interventions and analgesic delivery.

Conclusions: Because of low-certainty evidence and closely balanced benefits and harms, most recommendations are conditional. Patient preferences should drive clinical decisions. Policymaking, including that by payers, will require substantial debate and input from stakeholders. Randomized controlled trials and comparative-effectiveness studies are needed for chronic opioid therapy, nonopioid therapies, and nonpharmacological interventions.

Summary of Recommendations

Background

Pain causes significant morbidity for those living with sickle cell disease (SCD) and has a profoundly negative impact on patients' health-related quality of life (HRQOL). Pain manifests as both acute intermittent pain, chronic daily pain, and acute-on-chronic pain. Pain spans the life course and begins as

early as the first year of life. The emergence of chronic pain occurs with increasing age, and it has been estimated that 30% to 40% of adolescents and adults living with SCD suffer from chronic pain.^{1,2} The management of acute and chronic SCD pain is a major clinical challenge. This challenge is in part due to the complex and poorly understood pathophysiology that drives both acute and chronic pain. Mechanisms of SCD pain likely include components such as hypoxia-reperfusion injury, inflammation, increased red blood cell adhesion, and nervous system sensitization (central and peripheral).³⁻⁵ The causal mechanisms of acute and chronic pain likely differ, which further contributes to the challenges of effective pain treatment. US Food and Drug Administration–approved therapeutic interventions targeting the underlying biology of SCD pain are lacking, and this is an active area of investigation. The biology of SCD pain continues to be investigated in animal models and humans, and novel targets for analgesic therapy continue to emerge.⁵

In general, the optimal treatment of both acute and chronic pain requires an individualized approach that involves interdisciplinary care. This approach encompasses pharmacological, nonpharmacological, and integrative therapeutic interventions that are tailored to individual patient needs. There is no one-size-fits-all approach to optimal pain management. In the context of SCD, this interdisciplinary team includes providers from hematology, pain medicine, psychology/psychiatry, emergency medicine, nursing, and physical therapy among others. Therefore, the American Society of Hematology (ASH) guideline panel took an interdisciplinary approach to addressing specific questions related to the treatment of both acute and chronic pain, with special emphasis on the following areas: delivery of acute pain treatment including site of care and protocol used, nonopioid pharmacological therapy for acute and chronic pain, nonpharmacological therapy for acute and chronic pain, chronic opioid therapy (COT) for chronic pain, and chronic transfusion therapy.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the Mayo Evidence-Based Practice Research Program. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).⁶⁻⁹ The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach¹⁰⁻¹⁶ to assess the certainty in the evidence and formulate recommendations.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong (“the guideline panel recommends...”) or conditional (“the guideline panel suggests...”) and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.

- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the direction of the recommendation. On occasion, when the benefit between benefits and harms seems clear, a strong recommendation can be based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters or refines the recommendations.

Conditional recommendation

- For patients: a majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.
- For policymakers: policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on if an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.¹⁷ Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Use of a standardized protocol to treat acute SCD pain in the acute care setting

RECOMMENDATION 1A. For *adults and children* with SCD presenting to an acute care setting with acute pain related to SCD, the ASH guideline panel *recommends* rapid (within 1 hour of emergency department [ED] arrival) assessment and administration of analgesia with frequent reassessments (every 30-60 minutes) to optimize pain control (strong recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Non-IV routes of administration (eg, subcutaneous and intranasal) can facilitate rapid analgesic treatment.

RECOMMENDATION 1B. For *adults and children* with SCD presenting to an acute care setting with acute pain related to SCD for whom opioid therapy is indicated, the ASH guideline panel *suggests*

tailored opioid dosing based on consideration of baseline opioid therapy and prior effective therapy (*for adults*: conditional recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕○; *for children*: conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Individualized care plans, developed with acute care and SCD care providers, are treatment recommendations that include medications and doses that are effective for a given patient. These plans can be embedded in the electronic medical record and used to guide opioid dosing.
- For a minority of patients, frequent acute care treatment using individualized opioid dosing may be ineffective and detrimental to long-term care goals, and a more chronic care paradigm with other approaches may be needed.
- Patient preferences for acute-pain management should be incorporated into the shared decision-making process, and patient education on limitations and harms of opioid therapy should be included in the discussion.
- Adequate clinical infrastructure, including appropriate patient records, means of communicating between sites of care, and a multidisciplinary team with appropriate skills, is needed to create appropriate care plans.

Nonopioid pharmacological therapies for acute SCD pain

RECOMMENDATION 2A. For *adults and children* with acute pain related to SCD, the ASH guideline panel *suggests* a short course (5 to 7 days) of nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to opioids for acute pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- NSAIDs herein are defined broadly to include selective and nonselective cyclooxygenase (COX) inhibitors.
- Patient-specific assessment of harms, including but not limited to renal, vascular, and gastrointestinal toxicity, anticoagulation requirements, and cardiovascular disease, will help identify patients who are appropriate for NSAID therapy and tailor the selection of the drug/class of NSAID based on this risk profile.
- Patients specifically at increased risk of renal toxicity need to be identified. If comorbidities (eg, peptic ulcer disease, renal dysfunction, full-dose anticoagulation) are a significant risk factor, the mild potential benefit may not outweigh the risk.

GOOD PRACTICE STATEMENT. It is good practice to provide patient-centered education and surveillance related to NSAID toxicity, especially in patients with end-organ comorbidities, because long-term safety data for SCD are lacking, but vascular, bleeding, and renal risks may be elevated.

RECOMMENDATION 2B. For *adults and children* presenting for acute pain related to SCD, the ASH guideline panel *suggests against* corticosteroids for acute pain management (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Steroids should still be used when appropriate for the treatment of other medical indications such as asthma.
- Systemic corticosteroid exposure, particularly cessation of steroids, has been associated with rebound pain and other complications; therefore, the decision to use steroids for other medical indications should be made in collaboration with experts in SCD.

RECOMMENDATION 2C. For *adults and children* presenting with acute pain related to SCD who are hospitalized, the ASH guideline panel *suggests* a subanesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation assumes safe administration of subanesthetic ketamine infusions in the hospital inpatient unit in centers that have appropriate expertise to administer the drug.
- Recommended dose for subanesthetic (analgesic) infusion for acute exacerbation of SCD pain starts at 0.1 to 0.3 mg/kg per hour with a maximum of 1 mg/kg per hour.
- Currently, there is no standardized, widely accepted definition for the word refractory; therefore, whether pain is considered refractory is determined at the clinician's discretion.

RECOMMENDATION 2D. For *adults and children* presenting with acute pain related to SCD, the ASH guideline panel *suggests* regional anesthesia treatment approaches for localized pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Regional anesthesia in this context is defined as epidural or peripheral nerve catheter-delivered analgesia for abdominal, hip, or leg pain.
- The procedure needs to be technically feasible based on the anatomical location of the pain.
- A thorough explanation of the procedure as well as risks, benefits, and alternative options should be provided to patients and families before the procedure.
- The recommendation assumes administration of the procedure in a center that has appropriate resources and expertise.
- There is considerable uncertainty around optimal timing and indications for regional anesthesia interventions; however, the panel emphasized the importance of shared decision making based on the patient's knowledge of his or her own disease and course of pain-related complications and strategies that promote reduced opioid requirements, improved function, pain management, and reduced duration of hospitalization.

NO RECOMMENDATION. For *adults and children* who seek treatment of acute pain, the ASH guideline panel chooses not to offer a recommendation for or against IV fluids in addition to standard pharmacological management for the treatment of acute pain.

Remarks:

- The panel acknowledges that the risk of harm with IV fluids may be greater in adults than children because of deficiencies in cardiopulmonary function and other comorbid conditions.
- This nonrecommendation includes bolus infusions and infusions to maintain fluid balance requirements in addition to the types of fluids (eg, normal [0.9%] saline vs half-normal [0.45%] saline) that are used in these infusions.
- This nonrecommendation does not preclude the administration of fluids to patients with clinically significant dehydration.

Nonpharmacological therapies for acute SCD pain

RECOMMENDATION 3. For *adults and children* who seek treatment of acute pain, the ASH guideline panel *suggests* massage, yoga, transcutaneous electrical nerve stimulation (TENS), virtual reality (VR), and guided audiovisual (AV) relaxation in addition to standard pharmacological management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based on direct evidence from patients with SCD and indirect evidence largely from postoperative adult mixed surgical populations.
- Despite the evidence being primarily based on adult populations, there is low risk of harm in children. However, a tailored approach should be used that matches feasibility and acceptability for a given patient. Some interventions may not apply to younger children; therefore, the age of the patient should be considered, especially for interventions such as yoga and guided AV relaxation.
- Time requirements, financial costs, availability, and training of therapists for these types of treatments are important factors in treatment selection and should be discussed with patients in the course of shared decision making.

NO RECOMMENDATION. For *adults and children* who seek treatment of acute pain, the ASH guideline panel chooses not to offer a recommendation for or against acupuncture or biofeedback for the treatment of acute pain in addition to standard pharmacological management.

Remarks:

- If biofeedback and acupuncture are considered, a tailored approach is necessary that matches feasibility, acceptability, and patient experience and preference regarding these interventions for a given patient.
- Discussion with patients in the course of shared decision making needs to include important factors such as the time, financial costs, availability, and training of the therapists required to perform these treatments.

Pain management in an SCD-specific hospital-based acute care facility

RECOMMENDATION 4. For *adults and children* who develop acute pain episodes requiring hospital care, the ASH guideline panel *suggests* using SCD-specific hospital-based acute care facilities (ie, day hospitals and infusion centers, all with appropriate

expertise to evaluate, diagnose, and treat pain and other SCD complications) over typical ED-based care (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- This recommendation assumes that these hospital-based facilities have readily available code team coverage to ensure delivery of the safest care.
- From a hospital or system perspective, more detailed cost analyses would be warranted before deciding on implementation for a given institution. SCD-specific hospital-based acute care facilities tend to be cost effective to the extent that they reduce ED visits and admissions; however, overall acute care utilization may increase.
- Most of the evidence describing hospital-based acute care facilities places pain treatment in the context of complex SCD comprehensive care models. In these models, >1 intervention is likely driving the improvement and continuity in care.

Continuous basal opioid infusion for acute SCD pain treatment

NO RECOMMENDATION. For *children and adults* with SCD who seek treatment of acute pain in the hospital, the ASH guideline panel chooses not to offer a recommendation for or against basal opioid dosing in conjunction with on-demand dosing or scheduled intermittent dosing.

Remarks: For clarity, the panel defined the specific terms used as follows:

- Basal: continuous IV opioid infusion.
- On-demand dosing: opioid administered at an interval that relies on patients declaring their own need. Opioid can be administered via a patient-controlled IV analgesia pump or via an as-needed order for intermittent nurse-administered drug.
- Scheduled intermittent dosing: opioid administered on a timed schedule that does not rely on the patient asking for the drug.

Nonopioid pharmacological therapies for chronic pain in SCD with another identifiable cause

RECOMMENDATION 6A. For *adults* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel *suggests* use of duloxetine (and other serotonin and norepinephrine reuptake inhibitor [SNRI] medications, because there is evidence of a class effect) as an option for management, in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

RECOMMENDATION 6B. For *adults* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel *suggests* the use of NSAIDs as an option for management, in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

NO RECOMMENDATION. For *children* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel chooses not to offer a recommendation for or against the use of SNRIs and/or NSAIDs.

NO RECOMMENDATION. For *adults and children* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of leg ulcers, the ASH guideline panel chooses not to offer a recommendation for or against any specific nonopioid pharmacological management strategy.

Remarks:

- NSAIDs herein are defined broadly to include selective and nonselective COX inhibitors.
- There was a lack of both direct and indirect evidence for all-cause avascular necrosis nonsurgical pain management. Therefore, the panel chose to use osteoarthritis as an indirect evidence source, because it is a degenerative arthropathy with a reasonable evidence base. This evidence base is restricted to adults.
- Surgical and nonsurgical approaches to the treatment of the underlying cause of avascular necrosis were not the focus of this recommendation.

GOOD PRACTICE STATEMENT. It is good practice to provide patient-centered education and surveillance related to NSAID toxicity, especially in patients with end-organ comorbidities, because long-term safety data are lacking for SCD, but vascular, bleeding, and renal risks may be elevated.

GOOD PRACTICE STATEMENT. Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Nonopioid pharmacological therapies for chronic pain in SCD and no identifiable cause beyond SCD

RECOMMENDATION 7A. For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* SNRIs (eg, duloxetine and milnacipran) as options for pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD (with no identifiable cause beyond SCD).
- Antidepressants may increase the risk of suicidal ideation and behavior in children and adolescents with major depression disorder and other psychiatric disorders.
- The significant lack of pediatric data for the use of SNRIs for pain management could not support a recommendation for this age group.

RECOMMENDATION 7B. For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* tricyclic antidepressants (TCAs; eg, amitriptyline) as an option for pain management (conditional recommendation

based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD with no identifiable cause.
- Antidepressants may increase the risk of suicidal ideation and behavior in children and adolescents with major depression disorder and other psychiatric disorders.
- The significant lack of pediatric data for the use of TCAs for pain management could not support a recommendation for this age group.
- The increased adverse effect profile for this drug includes, but is not limited to, prolonged QT, orthostasis, cognitive impairment, dry mouth, and anticholinergic effects. These adverse effects should be considered and discussed with patients.

RECOMMENDATION 7C. For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* gabapentinoids (eg, pregabalin) as options for pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD with no identifiable cause.
- The significant lack of pediatric data for the use of gabapentinoids for pain management could not support a recommendation for this age group.

GOOD PRACTICE STATEMENT. Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Nonpharmacological therapies for chronic pain in SCD

RECOMMENDATION 8A. For *adults and children* with SCD who have chronic pain related to SCD, the ASH guideline panel *suggests* cognitive and behavioral pain management strategies in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- The cognitive or behavioral pain management strategy with the broadest evidence base is cognitive behavioral therapy (CBT). Other strategies considered by the panel with lower certainty in evidence include acceptance and commitment therapy (ACT), mindfulness-based treatments, coping skills training, and operant therapy.
- This recommendation is based mainly on indirect evidence. The treatments that have been tested in SCD are in children with

acute pain without establishing the presence of chronic pain or the intervention's effects on chronic pain. The outcomes assessed in SCD have not typically included pain intensity. The greater body of indirect evidence was drawn from the literature in individuals with fibromyalgia and nonspecific lower back pain.

- No standardized, manualized universally accepted version of CBT is available for SCD in either adults or children. This is a significant clinical and translational research need. Nonetheless, such strategies have shown broad applicability in pediatric and adult chronic noncancer pain.
- Interventions based on CBT, coping skills training, and guided imagery have some evidence base for SCD, although mainly in children and for episodic pain.
- In other conditions, these methods are believed to have low risks and are portable in that patients can use the skills learned on their own after treatment, possibly with intermittent booster sessions.
- Time, financial costs, availability, and training of therapists (ie, in chronic pain and SCD) and patient burden can be barriers to these types of psychological treatments that are being recommended.
- Cognitive and behavioral pain management strategies should be used in conjunction with other modalities as part of a comprehensive and multimodal pain management plan.
- Behavioral and cognitive strategies are optimal in a setting where the patient is motivated and there is access to appropriately trained personnel.

RECOMMENDATION 8B. For *adults* with SCD who have chronic pain related to SCD, the ASH guideline panel *suggests* other provider-delivered integrative approaches (eg, massage therapy and acupuncture) as available and as tolerated and conditional upon individual patient preference and response. These approaches should be delivered in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Time, financial costs, availability, and training of therapists (ie, chronic pain and SCD) and patient burden can be barriers to these types of treatments.
- There is currently a lack of evidence in children; however, some pediatric patients may be using these treatments at home.

NO RECOMMENDATION. For *adults and children* with SCD who have chronic pain related to SCD, the ASH guideline panel chooses not to offer a recommendation for or against a number of physical activities, exercise, or combined meditation/movement programs (including aerobic exercise, yoga, and Pilates) to improve pain and disability.

GOOD PRACTICE STATEMENT. Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Chronic opioid therapy for chronic pain in SCD

GOOD PRACTICE STATEMENT. It is good practice to deliver patient-centered education regarding the potential to develop chronic pain and the nonopioid pain treatment options that are outlined in recommendations 6, 7, and 8.

RECOMMENDATION 9A. For *adults and children* with SCD and emerging and/or recently developed chronic pain, the ASH guideline panel *suggests against* the initiation of COT unless pain is refractory to multiple other treatment modalities (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.
- In those whose pain has been refractory to multiple other interventions, COT should be considered after risk stratification using a validated tool, based on how well patients' SCD is managed, comprehensive assessment of behavioral risks (eg, risk factors for opioid misuse), implications of tolerance on the management of acute pain episodes, and other known adverse effects of opioids. Adverse events noted in other non-SCD patient populations are dose dependent and include increased risk of poor surgical outcomes, increased risk of motor vehicle collisions, myocardial infarction, bone fracture, and mortality. Patients on doses of >120 mg of morphine milligram equivalents (MME) are at risk for hormonal alterations, which can lead to sexual dysfunction. Doses >100 mg of MME are associated with a ninefold increase in risk of overdose compared with doses <20 mg of MME in general non-SCD pain populations.
- Failure criteria for a trial of COT should be discussed in the shared decision-making process, and alternative treatments in the case of failure and a plan for opioid cessation should be developed before initiation. Documentation of this discussion and the goals of care should be included in the medical record.
- The lowest effective opioid dose should be prescribed.
- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Providers should be aware that patients may inadvertently end up on COT if episodic pain is frequent enough that patients are receiving frequent opioid treatment of recurrent pain. Therefore, providers should make efforts to reduce or eliminate scheduled opioid doses between acute episodic pain events, which may reduce the likelihood of unintentional COT.

RECOMMENDATION 9B. For *adults and children* with chronic pain from SCD who are receiving COT, are functioning well, and have perceived benefit, the ASH guideline panel *suggests* shared decision making for continuation of COT (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.
- The benefit of COT in SCD is largely unknown, and the harms are established via indirect evidence (recommendation 9a, remark 2); therefore, shared decision making is essential and

may lead to continuation once risks of COT and tapering are explained.

- Function should be assessed from the shared patient/clinician perspective. The use of standardized patient-reported outcome tools that assess patient functioning is encouraged.
- COT is discussed as a class of drugs. Individual opioid drugs have different specific toxicity profiles and interactions with end-organ injury. Therefore, a review of the individual profile of each drug under consideration for use should be performed for a given patient.
- The lowest effective opioid dose should be prescribed.
- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Patients on COT require careful monitoring with regard to functional status and risk assessment for the development of aberrant opioid use and medical, social, behavioral, or psychological complications as a precursor to opioid dose reduction or weaning.
- The risk of adverse events related to COT rises as the total dose increases. Therefore, patients on high doses of opioids need close monitoring for complications and adverse effects.

RECOMMENDATION 9C. For *adults and children* with chronic pain from SCD who are receiving COT, are functioning poorly, or are at high risk for aberrant opioid use or toxicity, the ASH guideline panel *suggests against* continuation of COT (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.
- Collaboration with a pain specialist should be strongly considered for additional or alternative pain management strategies.
- Weaning and/or withdrawal from COT is potentially a higher-risk entity in patients with SCD (ie, risk of triggering vasoocclusive events or other medical complications) and should be done carefully.
- The other recommendations provided in this summary should be used for potential alternatives that could be part of a comprehensive pain management plan.
- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Acute pain events may still be treated with opioid analgesia if this serves the overall pain treatment plan, but this should be done in conjunction with the primary outpatient management team. Furthermore, nonopioid medications and integrative therapies should also be offered as outlined in prior recommendations.

GOOD PRACTICE STATEMENT. It is good practice to implement harm reduction strategies for patients on COT, including strongly considering coprescribing naloxone, avoiding coprescribing opioids and benzodiazepines, and prescribing the lowest effective opioid dose.

GOOD PRACTICE STATEMENT. It is good practice to consider collaboration with pain medicine specialists for the management of individuals living with SCD who have chronic pain.

GOOD PRACTICE STATEMENT. In cases in which the clinician has valid and substantial evidence of aberrant opioid use, it is good practice to consider consulting an addiction medicine physician.

GOOD PRACTICE STATEMENT. It is good practice to provide patient-centered education regarding the risks of COT.

GOOD PRACTICE STATEMENT. Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Chronic transfusion therapy for recurrent acute pain and/or chronic pain

RECOMMENDATION 10. For *adults and children* with SCD and recurrent acute pain, the ASH guideline panel *suggests against* chronic monthly transfusion therapy as a first-line strategy to prevent or reduce recurrent acute pain episodes (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- In unique circumstances when all other measures to control recurrent pain episodes have failed (eg, hydroxyurea, other disease modifying therapies) and when shared decision making can be fully applied, a trial of monthly transfusions may be reasonable.
- The decision should be influenced primarily by patient preference where patients appreciate the uncertainty in benefit over the burden and risks of monthly transfusion. Integration of education and informed shared decision making around initiation and/or cessation of chronic transfusion therapy is important.
- IV access and adherence to chelation and erythrocytapheresis are also considerations that could favor monthly transfusions in the exceptional circumstances noted above.
- The cessation of chronic transfusions can be associated with other SCD complications. Therefore, it is important to exercise caution if cessation of chronic transfusion is considered, including initiation of other disease-modifying therapies and increased surveillance.

NO RECOMMENDATION. For *adults and children* with chronic pain from SCD, the ASH guideline panel chooses not to offer a recommendation either for or against chronic monthly transfusion therapy as an option for pain management.

Values and preferences

Overall, the ASH guideline panel on the management of acute and chronic pain placed a higher value on outcomes related to pain relief and optimizing patient function encompassing improvements in patient-reported outcomes (ie, HRQOL) when making recommendations. Throughout the process, the panel members strongly considered the balance between benefits and harms for each intervention when making recommendations. Particular attention was paid to this balance in the context of both pediatric and adult age groups, because evidence was not always available for all ages. The panel placed a lower value on cost. The panel recognized that

variability likely exists in the context of values and preferences that pertain to these recommendations among both patients and providers. This variability is relevant when there is a lack of direct data to inform the discussion of these values and preferences. Furthermore, because most recommendations are conditional, shared decision making is required between patients and providers before a definitive decision on implementation of the considered therapies.

Introduction

Aims of these guidelines and specific objectives

The purpose and primary goals of these guidelines are to provide evidence-based recommendations to facilitate management of acute and chronic pain in individuals living with SCD. To achieve these goals, the ASH guideline panel reviewed and critically appraised the published literature and made evidence-based recommendations. Through improved provider and patient education regarding the available evidence and evidence-based recommendations, these guidelines aim to provide support for shared decision making that will result in improved patient functioning and decreased pain-related morbidity for individuals living with SCD.

The target audience includes patients and their caregivers, hematologists, general practitioners, internists, emergency medicine providers, and other clinicians and decision makers. Policy-makers interested in these guidelines include those involved in developing local, national, or international plans with the goals of optimizing pain management for individuals living with SCD and decreasing patient suffering. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

Pain causes significant morbidity for individuals living with SCD. Pain manifests as both acute and intermittent pain, chronic daily pain, and/or acute-on-chronic pain. Pain spans the life course of the disease and begins as early as the first year of life, and chronic pain emerges with increasing age. The management of pain for children and adults living with SCD is a major clinical challenge in part because of the complex biology of acute and chronic pain that is still not entirely understood and the lack of evidence on which to base recommendations. Furthermore, pain is a multidimensional disease manifestation and requires individualized care, meaning that there is no one-size-fits-all approach to pain management. To this end, optimal pain treatment requires an integrated approach of interdisciplinary care that incorporates both pharmacological and nonpharmacological interventions.

Currently, opioids constitute the mainstay of treatment of acute SCD pain when patients seek care in a health care setting. Opioids are also frequently used for the management of both acute and chronic pain at home. Despite the widespread use of COT for chronic pain, there is variability in practice, likely driven by the paucity of data to support or refute its use. The use and role of nonopioid pharmacological therapy and nonpharmacological therapies for the treatment of acute and chronic SCD pain have not been well studied. Therefore, these practice gaps and variability led the panel to evaluate the evidence for the efficacy and effectiveness of these pharmacological and nonpharmacological therapies for

Explanations and other considerations

These recommendations take into consideration acceptability, feasibility, cost effectiveness, resource use, and impact on health equity. The ASH guideline panel acknowledged variability in patient and provider knowledge as well as variability in their perceptions of harms vs benefits and other patient-important outcomes when developing these recommendations.

acute and chronic SCD pain. Furthermore, despite the widespread practice of using chronic transfusion therapy for prevention and treatment of recurrent acute and chronic pain, evidence-based recommendations do not exist for the indications for transfusion. Therefore, the panel also sought to evaluate the evidence for the efficacy and/or effectiveness of chronic transfusion therapy as a treatment of recurrent acute and chronic pain.

Care delivery of pain treatment (eg, site of care and protocol for opioid delivery) is also vital to optimal patient outcomes. The ED is the most common site of care delivery for acute pain treatment; however, alternative care delivery models, such as day hospitals and infusion clinics, have emerged. Their increasing use led the panel to evaluate the evidence for the impact of these models on outcomes important to patients. In addition to site of care, variability exists around how opioids are delivered for treatment of acute pain both in the acute care setting (eg, ED and day hospital) and during hospitalization. This variability led the panel to evaluate the evidence for protocols for opioid delivery including time to first dose, individualized dosing, and continuous basal IV opioid infusion as part of patient-controlled analgesia (PCA) during hospitalization.

The ASH guideline panel took a broad scope to the identification of questions that addressed the topics discussed above. The panel agreed that the guidelines needed to address both acute and chronic pain. The panel agreed that the final recommendations focused on acute and chronic pain should be distinct to reflect variation in the manifestations and etiology of these subclasses of pain that may require different treatment approaches. Furthermore, the panel agreed to address not only what intervention is delivered but also the protocol and site of care delivery (eg, ED, day hospital). Because optimal pain management is interdisciplinary, the panel addressed questions focused on opioid therapy, nonopioid pharmacological therapies, nonpharmacological and integrative therapies, and the role of chronic transfusion therapy. The panel had a general impression before formulating questions that a paucity of data existed in SCD for the important areas of interest identified by the panel. However, the panel did not limit questions based on potential availability of data. *There was panel consensus that it was vital to propose all important questions regardless of potentially available data to drive research for novel treatments for acute and chronic pain if deficiencies in the evidence base around these questions were identified.*

Definitions of acute and chronic pain

Clearly established a priori definitions of acute and chronic pain for individuals living with SCD were integral to the development of the questions, systematic review of the evidence, and formulation of

final recommendations. The definitions of acute and chronic pain that were agreed upon by the panel are outlined below.

Acute pain: pain that results in an unplanned visit to an acute care setting for treatment. An acute care setting was defined as ED, day hospital, infusion center, observation unit, acute pain center, or inpatient unit. The panel acknowledges that this definition may not encompass all acute pain that is experienced by individuals, because acute pain is often managed at home. However, for the basis of the evidence review for these guidelines, a decision had to be made that involved delivery of care in a health care setting.

Chronic pain: reports of ongoing pain present on most days over the past 6 months in either a single location or multiple locations.¹⁸ The panel agreed to define chronic pain using the “AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain.”¹⁸ These consensus-based definitions were established in collaboration with the American Pain Society and were based on frequency-based criteria similar to those used for the development of the International Classification of Headache Disorders classification system.^{18,19} These criteria also differentiate patients with chronic pain into subgroups based on SCD pain diagnostic modifiers as an attempt to encompass the varied etiology of chronic SCD pain. The panel designed questions and subsequent systematic reviews of the evidence to differentiate interventions that are most applicable to management of these different chronic pain subgroups. These subgroups are outlined below and are used as a basis for recommendations 6 and 7.

- Chronic SCD pain without contributory disease complications: chronic pain is more likely due to central or peripheral nervous system sensitization and has a nonidentifiable cause.
- Chronic SCD pain with contributory disease complications: chronic pain is end-organ related and has an identifiable cause (eg, avascular necrosis, leg ulcers).

The panel acknowledges that mixed-pain phenotypes exist where patients have both pain with an identifiable cause and pain without an identifiable cause. However, for the sake of the guidelines, the panel elected to focus on the 2 subgroups above for the recommendations, and it is likely that some patients could benefit from treatment of both pain subtypes simultaneously. This illustrates the complexity of providing comprehensive and multidisciplinary care for patients with chronic pain. Providers will need to use their clinical judgment to create an individualized treatment plan that addresses each patient’s unique needs.

Differentiation between pediatric and adult evidence and recommendations

Throughout the guideline process, the panel discussed the differences in the evidence base between pediatric and adult populations. In addition, the panel appraised the evidence for the age spectrum in the evidence-to-decision (EtD) framework and carefully discussed the harms and benefits for children and adolescents if adult data were extrapolated to a recommendation that included children. These differences are reflected in the final recommendations where the population is clearly identified in the recommendation (ie, “In adults *and* children with SCD...” or “In adults with SCD...”). In addition, these differences are reflected in the distinction made regarding strength of the recommendation and

Table 1. Questions prioritized by the ASH guideline panel on management of acute and chronic pain

Prioritized questions
Q1. In children and adults who seek treatment of acute pain, should a standardized protocol be used that includes (1) reduced time to first dose (<1 h from arrival) in addition to more frequent reassessment and dosing of pain medication (<30 min) and (2) tailored dosing (vs weight-based dosing)?
Q2. Should nonopioid pharmacological therapies either in addition to or instead of opioids or other usual care interventions be used for the treatment of acute pain in children and adults with SCD?
Q3. Should nonpharmacological therapies in addition to pharmacological therapies be used for the treatment of acute pain in children and adults with SCD?
Q4. Should a hospital-based entity such as a day hospital or observation unit compared with regular ED care be used for children and adults with SCD who seek treatment of acute pain?
Q5. Should a combination of continuous basal opioid infusion with on-demand dosing vs on-demand opioid dosing alone or scheduled intermittent opioid dosing be used for children and adults with SCD hospitalized for the treatment of acute pain?
Q6. Should nonopioid pharmacological therapy, either in addition to or instead of opioids or other usual care interventions, be used for children and adults with SCD and chronic pain with another identifiable cause (eg, avascular necrosis, leg ulcers)?
Q7. Should nonopioid pharmacological therapy, either in addition to or instead of opioids or other usual care interventions, be used for children and adults with SCD and chronic pain with no identifiable cause beyond SCD?
Q8. Should nonpharmacological therapies be used in addition to pharmacological therapy for the treatment of chronic pain in children and adults with SCD?
Q9. Should chronic opioid therapy vs no chronic opioid therapy or periodic opioid therapy be used in patients with SCD who have chronic pain?
Q10. Should chronic monthly transfusion therapy to suppress hemoglobin S levels of <30% vs no transfusions or on-demand transfusions be used for children and adults with SCD who have recurrent acute pain and/or chronic pain?

quality of the evidence. Technical remarks also include information pertinent to specific age groups. Therefore, users of these guidelines should pay particular attention to the identified population for each recommendation and technical remarks to avoid extrapolating a recommendation to an unintended age group.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.¹⁰⁻¹⁶ The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN–McMaster Guideline Development Checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.⁶⁻⁹

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 4 other guideline panels (addressing other aspects of SCD) by ASH and the Mayo Evidence-Based Practice Research Center (funded by ASH under a paid agreement). Project oversight was provided by a coordination panel, which reported to the ASH Guideline Oversight Subcommittee. ASH vetted and appointed individuals to the guideline panel. The Mayo Center vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process including the use of the GRADE approach.

Table 2. Outcomes prioritized by the ASH guideline panel on management of acute and chronic pain

Critical outcomes for decision making
Q1.
No. of analgesic doses administered
Time to first analgesic dose
Time to second analgesic dose
Total MME administered
Rate of hospitalization
Proportion discharged home from the ED
Length of stay in ED
Proportion admitted to observation unit
Improved pain intensity defined as percentage of patients who achieve $\geq 30\%$ reduction in pain score or ≥ 2 -point reduction in pain score on a standard NRS or ≥ 20 -mm reduction in VAS score from first score to last score
Percentage of patients who achieve reduction in pain score back to baseline at disposition
Satisfaction with care
Rate of respiratory depression events
Rate of hypoxic events
Rate of naloxone administrations
Q2.
Total MME consumed
Improved pain intensity defined as percentage of patients who achieve $\geq 30\%$ reduction in pain score or ≥ 2 -point reduction in pain score on a standard NRS or ≥ 20 -mm reduction in VAS score from first score to last score
Length of stay
Time to reduction in pain intensity
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Acute functional outcome (Youth Acute Pain Functional Ability Questionnaire)
Patient satisfaction
Opioid-related adverse effects
PGIC
CGIC
Q3.
Improved pain intensity, defined as percentage of patients who achieve $\geq 30\%$ reduction in pain score or ≥ 2 -point reduction in pain score on a standard NRS or ≥ 20 -mm reduction in VAS score from first score to last score
Pain coping strategies (eg, negative thinking, stress)
Total MME consumed
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Length of stay
Return to baseline pain
Q4.
Wait times for care
Time to first analgesic dose
Time between analgesic doses
Need for ED care
Hospitalizations
Missed school/work days

Table 2. (continued)

Critical outcomes for decision making
Improved pain intensity, defined as percentage of patients who achieve $\geq 30\%$ reduction in pain score or ≥ 2 -point reduction in pain score on a standard NRS or ≥ 20 -mm reduction in VAS score from first score to last score
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Cost
Patient satisfaction with care
Q5.
Improved pain intensity, defined as percentage of patients who achieve $\geq 30\%$ reduction in pain score or ≥ 2 -point reduction in pain score on a standard NRS or ≥ 20 -mm reduction in VAS score from first score to last score
Length of stay
Time to reduction in pain intensity
Patient satisfaction with care
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Acute functional outcome (Youth Acute Pain Functional Ability questionnaire)
Total opioid consumed in a 24-h period (ie, either oral or parenteral milligram opioid equivalents)
PGIC
CGIC
Rate of respiratory depression events
Rate of hypoxic events
Rate of naloxone administrations
Rate of acute chest events
Q6.
Health care encounters for pain
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Functional outcomes
Sleep
Mood (anxiety, depression)
Reduction in chronic opioids (daily dose of MME)
Pain intensity
PGIC
CGIC
Q7.
Health care encounters for pain
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Functional outcomes
Sleep
Mood (anxiety, depression)
Reduction in chronic opioids (daily dose of MME)
Pain intensity
PGIC
CGIC
Q8.
Pain intensity
Pain coping strategies (eg, negative thinking, stress)

CFIC, clinician global impression of change; NRS, numerical rating scale; PGIC, patient global impression of change; VAS, visual analogue scale.

Table 2. (continued)

Critical outcomes for decision making
Reduction in chronic opioids (daily dose of MME)
Health care encounters for pain
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Functional outcomes
Sleep
Mood (anxiety, depression)
PGIC
CGIC
Q9.
Long-term benefit (pain relief)
Long-term harm (defined broadly)
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Functional outcomes
Opioid-induced hyperalgesia
Health care encounters for pain
Hospitalization rate
Sleep
Mood (anxiety, depression)
Q10.
Health care encounters for pain
HRQOL (general domains and pain-specific domains, including pain interference and pain behavior)
Functional outcomes
Sleep
Mood (anxiety, depression)
Reduction in chronic opioids (daily dose of MME)
Pain intensity
PGIC
CGIC

CFIC, clinician global impression of change; NRS, numerical rating scale; PGIC, patient global impression of change; VAS, visual analogue scale.

The membership of the panels and the Mayo Center team is described in Supplement 1.

The panel included representative physicians from pediatric and adult hematology, pediatric and adult pain medicine, psychiatry, and emergency medicine and a doctoral nurse practitioner, who all had clinical and research expertise on the guideline topic. The panel also included 2 patient representatives. One cochair was a content expert; the other cochair was an emergency medicine physician and expert in guideline development methodology.

In addition to synthesizing evidence systematically, the Mayo Center supported the guideline development process, including determining methods, preparing meeting materials, and participating in panel discussions of evidence. The panel's work was performed using Web-based tools (www.surveymonkey.com and www.gradepr.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representatives received honoraria of \$100 per day for in-person meetings and \$25 per conference call. The panelists received no other payments. Through the Mayo Clinic Evidence-Based Practice Research Program, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed through disclosure, panel composition, and recusal, according to ASH policies based on recommendations of the Institute of Medicine²⁰ and the GIN.⁹ Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the guideline panel, including the cochairs, had no such conflicts. None of the Mayo-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was used to manage conflicts of interest.^{9,21-23} During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) or the direction or strength of the recommendation. The EtD framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2019, after the guideline panel had agreed on recommendations, 1 panelist disclosed that during the guideline development process, he had received direct payments from a company that could be affected by the guidelines. This disclosure occurred after the panel had agreed on recommendations; therefore, the individual was not recused. Members of the ASH Guideline Oversight Subcommittee reviewed the guidelines in relation to this late disclosure and agreed that the conflict was unlikely to have influenced any of the recommendations.

Supplement 2 provides the complete disclosure-of-interests forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years before appointment; in part B, indirect financial interests; and in part C, not mainly financial interests. Part D describes new interests disclosed by individuals

Table 3. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	A majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplement 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel met in person and via conference calls to generate potential questions to address. The panel then used an iterative process to prioritize the 10 questions described in Table 1. The process allowed for a maximum of 10 questions to be addressed.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.²⁴ In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach.²⁴ While acknowledging considerable variation in the impact on patient outcomes, the panel considered the outcomes in Table 2 critical for clinical decision making across questions.

Evidence review and development of recommendations

For each guideline question, the Mayo Center prepared a GRADE EtD framework using the GRADEpro Guideline Development Tool (www.gradepro.org).^{10,11,16} The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence.

Literature searches conducted for the systematic reviews are presented as supplemental File 4. Searches for direct evidence were completed in August 2017. The search for question 4 was updated in May 2018. Searches for indirect evidence were performed in January 2019. Abstracts that did not result in peer-reviewed published manuscripts were not included in the evidence

profiles. From 2017 through development of this report, we did not formally search for but also did not informally identify important new studies that would have changed the direction or strength of any of the recommendations.

Under the direction of the Mayo Center, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk-of-bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.^{10,11,16} Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, imprecision, inconsistency, indirectness, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.¹²⁻¹⁴ Within this report, these categories are represented by the symbols, as follows:

- ⊕⊕⊕⊕ High certainty in the evidence about effects
- ⊕⊕⊕○ Moderate certainty in the evidence about effects
- ⊕⊕○○ Low certainty in the evidence about effects
- ⊕○○○ Very low certainty in the evidence about effects

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.¹²⁻¹⁴

For some questions, a systematic search identified few or no studies of patients with SCD. For these questions, the panel

considered indirect evidence from other populations. This was operationalized as follows. First, the panel reached consensus via online survey and discussion on conference calls about which questions could be addressed by indirect evidence. Next, the panel agreed on pain conditions for selected questions that most closely parallel acute and chronic pain in SCD based on similarities to the biology or experience of individuals with SCD. Supplement 5 includes the online survey that was completed independently by each panel member to reach consensus. The review team then searched for systematic reviews of pain interventions in these populations. Following a standard used by some guideline developers,²⁵ the panel offered a recommendation based on indirect evidence only if it could be supported by a systematic review and/or meta-analysis that included ≥ 5 studies. The panel did not base any recommendations on single studies from other indirect populations. In accordance with the GRADE approach, the body of evidence supporting such recommendations was downgraded, as applicable, for indirectness.

During 2 separate 2-day in-person meetings and supplemented by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty of the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly considered the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. The approach is described in detail in the accompanying article describing the methods of development.²⁶

Interpretation of strong and conditional recommendations

The recommendations are labeled as either strong or conditional according to the GRADE approach. The words “the ASH guideline panel recommends” are used for strong recommendations, and “the ASH guideline panel suggests” for conditional recommendations. Table 3 provide GRADE’s interpretation of strong and conditional recommendations by patients, clinicians, health care policymakers, and researchers.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.¹⁷ Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 10 April to 13 May 2019 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public.

Eighteen individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 25 February 2020, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed, and on 28 February 2020, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by the journal *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions based on the clinical presentation of each individual patient, ideally through a shared process that considers the patient’s values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by forthcoming decision aids.

Recommendations

Use of standardized protocols to treat acute SCD pain in the acute care setting

In children and adults who seek treatment of acute pain, should a standardized protocol be used that includes (1) reduced time to first dose (<1 hour from arrival) in addition to more frequent reassessment and dosing of pain medication (<30 minutes) and (2) tailored dosing (vs weight-based dosing)?

Recommendation 1a

For adults and children with SCD presenting to an acute care setting with acute pain related to SCD, the ASH guideline panel *recommends* rapid (within 1 hour of ED arrival) assessment and administration of analgesia with frequent reassessments (every 30 to 60 minutes) to optimize pain control (strong recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Non-IV routes of administration (eg, subcutaneous and intranasal) can facilitate rapid analgesic treatment.

Recommendation 1b

For adults and children with SCD presenting to an acute care setting with acute pain related to SCD for whom opioid therapy is indicated, the ASH guideline panel suggests tailored opioid dosing based on consideration of baseline opioid therapy and prior effective therapy (for adults: conditional recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕○; for children: conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Individualized care plans, developed with acute care and SCD care providers, are treatment recommendations that include medications and doses that are effective for a given patient. These plans can be embedded in the electronic medical record and used to guide opioid dosing.
- For a minority of patients, frequent acute care treatment using individualized opioid dosing may be ineffective and detrimental to long-term care goals, and a more chronic care paradigm with other approaches may be needed.
- Patient preferences for acute pain management should be incorporated into the shared decision-making process, and patient education on limitations and harms of opioid therapy should be included in the discussion.
- Adequate clinical infrastructure, including appropriate patient records, means of communicating between sites of care, and a multidisciplinary team with appropriate skills, is needed to create appropriate care plans.

Specific background. Acute episodes of SCD pain often result in ED visits. Treatment of SCD pain in the ED is continually cited by patients, caregivers, and other stakeholders as an area in need of improvement.²⁷⁻³⁴ Of particular concern is the high degree of variability in ED pain care between institutions and even between visits within the same institution. Currently, there is no standardized protocol for acute pain treatment that incorporates rapid treatment, frequent reassessments, and optimal opioid dosing to promptly and most effectively treat acute SCD pain. The panel reviewed the evidence to determine if recommendations could be made in 3 areas of ED pain care: (1) timing of the first dose of analgesia, (2) timing of reassessments and repeat doses of analgesia, and (3) use of tailored vs weight-based dosing of opioids in the ED.

Summary of the evidence. The systematic review identified 3 studies that met the search criteria: 1 randomized controlled trial (RCT),³⁵ 1 post hoc analysis of data from an RCT,³⁶ and 1 observational study.³⁷ The RCT was a 2-center pilot randomized trial comparing 2 opioid dosing strategies for acute SCD pain: weight based vs patient specific. Although the trial was small, participants in the patient-specific protocol had greater improvements in pain scores during their ED visits and lower rates of hospital admission.³⁵ The post hoc RCT study was a secondary analysis of an RCT that compared magnesium with placebo as an adjuvant treatment of acute SCD pain. This study found no association between early administration of opioids (≤60 minutes) and hospital length of stay or HRQOL. Finally, the observational study was a pre-post analysis of a quality improvement intervention to reduce the time to first analgesic for adult patients with SCD presenting to the ED for

treatment of acute pain. This study was unable to assess for an impact on utilization or patient-reported outcomes; however, it did demonstrate the challenges with implementation of efforts to facilitate faster analgesia in the ED. For example, the total wait time from triage to analgesic administration actually significantly increased after the quality improvement initiative was initiated.

Benefits. The potential benefits of rapid analgesia and tailored pain dosing are moderate. The panel agreed that the potential benefit of avoiding a hospital admission was important, even if the magnitude of the effect were small, because every avoided admission would make a large difference in a patient's life. The panel also noted that another benefit of rapid evaluation and analgesia is that other serious conditions that can occur in patients with SCD in the context of acute pain have the potential to be identified sooner during a patient's visit. Anxiety from waiting for pain treatment can increase pain, thereby creating a vicious cycle. Finally, the panel noted that there is a theoretical risk of developing chronic pain as a result of recurrent, inadequately treated pain.

Harms and burden. Harms were identified as trivial. There were no reported adverse events in the included studies. Tanabe et al³⁵ used a conservative algorithm to create tailored opioid doses, which may have reduced the occurrence of opioid-related adverse events. The panel did note 2 theoretical concerns of rapid treatment and tailored dosing: (1) rapid pain treatment and higher doses could increase euphoria and the risk of opioid tolerance, and (2) higher opioid dosing could increase perceptions of opioid misuse. The panel determined that both theoretical concerns had no supporting evidence and that these concerns should not affect the decision to improve SCD analgesia in the ED. Finally, the pathway used by Tanabe et al³⁵ caused an increased logistical burden. This was considered a barrier to implementation rather than a harm.

Rationale and key drivers for recommendations. The balance of benefits vs harms favors rapid initiation of opioids, frequent reassessments between treatments, and tailored opioid dosing. The panel identified only trivial undesirable effects of the interventions and found that the main barriers to implementation are related to logistical burdens. Although the evidence was limited, the panel noted that the 1 RCT rather conclusively demonstrated a benefit for tailored dosing. The panel noted that rapid treatment of all medical conditions is a general goal of acute care, which is so self-evident that additional evidence may not be needed to support rapid treatment of SCD pain, and that conducting an RCT to further support this recommendation would be unethical. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepro.org/profile/f96aff846a36b5bf8af439fd8555f123>.

Other EtD criteria and considerations. The panel agreed that there is potential for moderate to large cost savings associated with reducing the frequency of hospital admissions for SCD pain. In other diseases, clinical pathways are thought to be cost effective. Although there are no data regarding the costs of implementation of the recommended pain treatment pathway, and substantial resources may be required, it was generally concluded that all aspects of the interventions were both ethically and medically indicated. Regarding rapid analgesia, the panel considered a door-to-analgesia time of 60 minutes, which balances timeliness of analgesia delivery and feasibility in the ED setting.

Conclusions and research needs for these recommendations.

The panel concluded that there is low-certainty evidence to support rapid analgesia, frequent reassessments, and tailored dosing for acute SCD pain. Despite the limited amount of RCT data, there was consensus that harms were trivial, benefits were moderate, and implementation was likely both acceptable and ethical. For recommendation 1a, a strong recommendation was issued despite low-certainty evidence because although there was uncertain benefit of more rapid and frequent delivery of analgesia, there is certain, unequivocal harm to patients with delay in pain treatment. RCTs comparing delayed analgesia and infrequent assessment were considered unethical. With that context, the panel considered existing quality improvement research and evidence of improved patient satisfaction^{38,39} to be sufficient evidence for a strong recommendation.

The panel identified the following additional areas of research that are needed: (1) additional research focused on patients' values and preferences in addition to patient-reported outcomes, (2) dissemination and implementation research to assess and address the system-level barriers and facilitators to pain treatment delivery in the ED, and (3) research focused on the role of delivery of nonopioid analgesic alternatives to opioid analgesia for acute pain management in the ED.

Nonopioid pharmacological therapies for acute SCD pain

Should nonopioid pharmacological therapies either in addition to or instead of opioids or other usual care interventions be used for the treatment of acute pain in children and adults with SCD?

Recommendation 2a

For *adults and children* with acute pain related to SCD, the ASH guideline panel *suggests* a short course (5 to 7 days) of NSAIDs in addition to opioids for acute pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- NSAIDs herein are defined broadly to include selective and nonselective COX inhibitors.
- Patient-specific assessment of harms, including but not limited to renal, vascular, and gastrointestinal toxicity, anticoagulation requirements, and cardiovascular disease, will help identify patients who are appropriate for NSAID therapy and tailor the selection of the drug/class of NSAID based on this risk profile.
- Patients specifically at increased risk of renal toxicity need to be identified. If comorbidities (eg, peptic ulcer disease, renal dysfunction, full-dose anticoagulation) are a significant risk factor, the mild potential benefit may not outweigh the risk.

Good practice statement. It is good practice to provide patient-centered education and surveillance related to NSAID toxicity, especially in patients with end-organ comorbidities, because long-term safety data for SCD are lacking, but vascular, bleeding, and renal risks may be elevated.

Recommendation 2b

For *adults and children* presenting for acute pain related to SCD, the ASH guideline panel *suggests against* corticosteroids for acute pain management (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- Steroids should still be used when appropriate for the treatment of other medical indications such as asthma.
- Systemic corticosteroid exposure, particularly cessation of steroids, has been associated with rebound pain and other complications; therefore, the decision to use steroids for other medical indications should be made in collaboration with experts in SCD.

Recommendation 2c

For *adults and children* presenting with acute pain related to SCD who are hospitalized, the ASH guideline panel *suggests* a subanesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation assumes safe administration of subanesthetic ketamine infusions in the hospital inpatient unit in centers that have appropriate expertise to administer the drug.
- Recommended dose for subanesthetic (analgesic) infusion for acute exacerbation of SCD pain starts at 0.1 to 0.3 mg/kg per hour with a maximum of 1 mg/kg per hour.
- Currently, there is no standardized, widely accepted definition for the word refractory; therefore, whether pain is considered refractory is determined at the clinician's discretion.

Recommendation 2d

For *adults and children* presenting with acute pain related to SCD, the ASH guideline panel *suggests* regional anesthesia treatment approaches for localized pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Regional anesthesia in this context is defined as epidural or peripheral nerve catheter-delivered analgesia for abdominal, hip, or leg pain.
- The procedure needs to be technically feasible based on the anatomical location of the pain.
- A thorough explanation of the procedure as well as risks, benefits, and alternative options should be provided to patients and families before the procedure. Assessment of risk and whether the patient is an appropriate candidate for this approach includes careful review of prescribed

concomitant medications that may increase risk of bleeding (eg, antiplatelet therapy, anticoagulation).

- The recommendation assumes administration of the procedure in a center that has appropriate resources and expertise.
- There is considerable uncertainty around optimal timing and indications for regional anesthesia interventions; however, the panel emphasized the importance of shared decision making based on the patient's knowledge of his or her own disease and course of pain-related complications and strategies that promote reduced opioid requirements, improved function, pain management, and reduced duration of hospitalization.

No recommendation

For *adults and children* who seek treatment of acute pain, the ASH guideline panel chooses not to offer a recommendation for or against IV fluids in addition to standard pharmacological management for the treatment of acute pain.

Remarks:

- This recommendation does not preclude the administration of fluids to patients with clinically significant dehydration to reestablish a euvolemic state.
- The panel acknowledges that the risk of harm with IV fluids may be greater in adults than children because of deficiencies in cardiopulmonary function and other comorbid conditions.
- This nonrecommendation includes bolus infusions and infusions to maintain fluid balance requirements in addition to the types of fluids (eg, normal [0.9%] saline vs half-normal [0.45%] saline) that are used in these infusions.

Specific background. Opioids have been the mainstay for the treatment of acute pain related to SCD. Although they frequently reduce pain, some patients do not respond to opioid therapy alone. In addition, the tenets of appropriate management of acute pain include multimodal analgesia. Given the recurrent episodes of acute pain that individuals with SCD endure, they are at risk for opioid-related adverse effects, tolerance, and aberrant opioid use. In addition, given the short- and long-term risks of opioids, it is appropriate to minimize opioid exposure. Emerging evidence also supports the concept that pronociceptive effects of opioids (sometimes referred to as opioid-induced hyperalgesia) may complicate pain treatment. Although most patients do not use opioids chronically, 1 pathway to reduce the opioid burden would be to provide nonopioid analgesics to treat acute pain with the goal of reducing the total dose and duration of exposure while maintaining or improving analgesia. Recently, there has been a greater understanding of the complex nature of pain in SCD such that better definitions of acute pain, chronic pain, and acute-on-chronic pain have emerged.^{18,40} Most studies in this review predated these definitions. The panel sought to systematically review the existing data and evidence to support the use of nonopioid pharmacological therapies (ie, NSAIDs, corticosteroids, subanesthetic ketamine, regional anesthesia, and IV fluids) in addition to opioids alone in the treatment of acute pain in SCD. Evidence for or against 4 therapeutic options

was identified by the systematic review of evidence: NSAIDs, corticosteroids, subanesthetic ketamine, and regional anesthesia. The panel did not identify any evidence in a systematic review of the evidence for the use of IV fluids in addition to pharmacological management of acute pain. The impact of these therapies on patient-centered outcomes such as reduced pain intensity, reduction in length of stay, improved QOL, reduction in opioid utilization, and reduction in opioid-related adverse effects was evaluated.

Recommendation 2a: NSAIDs for treatment of acute pain

SUMMARY OF THE EVIDENCE. The systematic review identified 6 studies in the direct literature that addressed the use of NSAIDs in patients with SCD. Of these studies, there were 4 RCTs, 1 case series, and 1 safety study. Evidence for the following outcomes existed: (1) pain intensity: decreased pain compared with the opioid meperidine in the ED setting,⁴¹ decreased pain when used alone in the ED setting,⁴² and decreased pain in the inpatient setting⁴³ (2 studies failed to show decreased pain in an inpatient setting^{44,45}); (2) length of stay: 1 study found decreased length of stay,⁴³ and another failed to show a difference in length of stay⁴⁵; and (3) reduction in opioid utilization: elimination of opioid utilization in the ED setting⁴² and reduction of opioid use in the inpatient setting.⁴³ Two studies did not show a reduction in opioid utilization in the inpatient setting.^{44,45} There were no studies that addressed some of the a priori–defined patient-centered outcomes, including HRQOL, satisfaction with care, and missed days of school or work. The studies were conflicting and heterogeneous, with small sample sizes; therefore, the recommendation is conditional based on low to moderate certainty in the evidence about effects.

BENEFITS. The potential benefits of NSAID use in acute pain in SCD are low to moderate and include improved pain control, reduced opioid utilization, and decreased length of stay.

HARMS AND BURDEN. The potential risks associated with NSAID use in acute SCD pain include nephrotoxicity, gastrointestinal disorders, and bleeding. In a single retrospective review of 197 children/adolescents admitted for acute pain, 33 had evidence of acute kidney injury.⁴⁶ Among patients who received ketorolac for pain, both total days and doses of ketorolac were associated with acute kidney injury. There were no other studies identified that investigated the harms of NSAID use specifically in individuals with SCD. The panel concluded that the risks of NSAID use in the general population also apply to individuals with SCD, and these are outlined in remarks 2 and 3 above.

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. Overall, the balance of effects favors the intervention. However, NSAIDs should be used cautiously in this population given the risk of kidney injury and the low certainty in the data. Therefore, balance of benefits and harms should be discussed in the context of each patient.

Recommendation 2b: against corticosteroids for treatment of acute pain

SUMMARY OF THE EVIDENCE. The systematic review identified 1 RCT (36 participants, 56 pain episodes) from the direct evidence that addressed the use of corticosteroids in children and adolescents (age <21 years) with SCD hospitalized for acute pain treatment.⁴⁷ Evidence for the following outcomes existed in this RCT: (1) length of stay: there was a decrease in length of stay in conjunction with opioids and (2) opioid utilization: the study failed to demonstrate reduced opioid utilization. There were no studies that addressed

some of the a priori–defined patient-centered outcomes, including pain, HRQOL, satisfaction with care, and missed days of school or work.

BENEFITS. The potential benefits of steroid use in acute pain in SCD include decreased length of stay.

HARMS AND BURDEN. In this single RCT discussed above, the risk of rehospitalization increased with steroid exposure.⁴⁷ In addition, the potential risks associated with steroid use in acute pain in SCD include those known in other patient groups, such as those with gastrointestinal disorders and immunosuppression.

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. Overall, the balance of effects does not favor the intervention given the risk of rehospitalization.

Recommendation 2c: subanesthetic ketamine for treatment of acute pain

SUMMARY OF THE EVIDENCE. The systematic review identified 5 studies in the direct evidence that addressed the use of subanesthetic ketamine in patients hospitalized for the treatment of acute SCD pain. Of these studies, there was 1 RCT (n = 240) addressing morphine vs ketamine,⁴⁸ 3 case series (n = 16),⁴⁹⁻⁵¹ and 1 cohort study (360 patients total, 181 with SCD).⁵² In all studies except for the RCT, ketamine was used primarily as an adjunctive analgesic therapy in patients not improving on opioid therapy. Evidence for the following outcomes existed: (1) reduced opioid utilization^{50,52} and (2) pain: there was a reduced pain score with adjunctive ketamine infusion^{49,50,52} and a similar reduction in pain compared with morphine.⁴⁸ There were no studies that addressed some of the a priori–defined patient-centered outcomes, including length of stay, HRQOL, satisfaction with care, and missed days of school or work. The studies were mostly retrospective and heterogeneous and had low sample sizes. Therefore, the recommendation is conditional based on low to moderate certainty in the evidence about effects.

BENEFITS. The potential benefits of subanesthetic ketamine infusions for the treatment of acute pain in hospitalized patients are small to moderate and include improved pain control and reduced opioid utilization. Recommended dose for subanesthetic (analgesic) infusion for acute exacerbation of SCD pain starts at 0.1 to 0.3 mg/kg per hour, with a maximum of 1 mg/kg per hour.^{53,54}

HARMS AND BURDEN. The included studies contain reports of nystagmus, visual hallucinations, dizziness, and dysphoria in patients with SCD who received ketamine. The additional potential risks associated with subanesthetic ketamine infusions in hospitalized patients with acute SCD pain include somnolence, dysphoria, and diversion. There is also a need for experienced practitioners to administer the drug safely.

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. Overall, the balance of effects favors the intervention. However, subanesthetic ketamine should be used cautiously in this population and in patients for whom first-line treatment (ie, opioids) has failed or in patients who wish to avoid opioid analgesia. Because of the absence of high-quality data and overall low to moderate certainty in the evidence about effects, the recommendation is conditional.

Recommendation 2d: regional anesthesia for treatment of acute pain

SUMMARY OF THE EVIDENCE. The systematic review identified 2 studies from the direct evidence that addressed the use of regional anesthesia treatment approaches for localized pain in patients with

SCD^{55,56} and 3 systematic reviews⁵⁷⁻⁵⁹ from the indirect evidence. Of the 2 studies from the direct evidence, both were retrospective case series (n = 20), and the indirect evidence included systematic reviews and meta-analyses of patients with hip fracture, postoperative pain, and labor pain. Data in the direct evidence included (1) reduced opioid utilization⁵⁵ and (2) reduced pain.^{55,56} Data for outcomes in the indirect evidence included the following: (1) pain: improved pain control compared with opioids in postoperative pain,⁵⁹ improved pain control compared with other methods in labor pain,⁵⁸ and improved pain control in hip fracture⁵⁷; (2) reduced opioid utilization: reduced supplemental analgesia in hip fracture⁵⁷; and (3) satisfaction with care: a higher proportion of women with labor pain rated their satisfaction with pain relief as excellent or very good.⁵⁸ There were no studies that addressed some of the a priori–defined patient-centered outcomes, including HRQOL and missed days of school or work. The studies were heterogeneous and relied on both direct and indirect evidence, with small sample sizes in the direct-evidence group. Therefore, the recommendation is conditional based on the low certainty in the evidence about effects.

BENEFITS. The potential benefits of regional anesthesia use in the treatment of acute pain in SCD are small and include improved pain control, reduced opioid utilization, and improved patient satisfaction.

HARMS AND BURDEN. Complications noted in the direct evidence include, fever, postdural puncture headache, epidural dislodgement, and failure to obtain sensory blockade. The potential risks associated with regional anesthetic use in SCD patients, as in other populations, include hypotension, motor blockade, fever, infection, and urinary retention. In woman in labor receiving epidural anesthesia, the rate of motor blockade is almost 20%.⁵⁸

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. Overall, the balance of effects favors the intervention. However, because of the absence of high-quality data for patients with SCD, regional anesthesia should be used only in centers with the appropriate expertise, in inpatients with localized pain that is amenable to a regional approach, and in patients for whom first-line treatment (ie, opioids) has failed or who wish to avoid opioid analgesia.

Other EtD criteria and considerations for recommendations 2a to 2d. The panel agreed that identifying nonopioid pharmacological therapies that have benefit for the treatment of acute pain in patients with SCD was a priority. The panel felt that patients and caregivers place a high value on treatments for acute pain that have the potential to be effective and opioid sparing. The lack of perceived efficacy of opioids for acute SCD pain and the potential for recurrent or chronic opioid use and the development of tolerance, dependence, addiction, and chronic pain were discussed by the panel. Unfortunately, a majority of interventions were supported by evidence that was of low or very low certainty in the effects. In addition, there were no data on cost effectiveness for the interventions considered. Feasibility is affected by resource requirements, including knowledge and technical requirements, which are variable for the interventions and directly affect health equity and acceptability. For instance, some institutions do not allow administration of subanesthetic ketamine infusions on a general medical floor (ie, patients require intensive care unit placement) and allow administration of the drug only by pain medicine physicians or anesthesiologists,

thus making this intervention not available in all institutions. In addition, regional anesthesia approaches may not be available to all patients, because they require an anesthesiologist to administer. Overall, because these are being recommended as second-line therapies, the overall effect on reduced health equity is likely small. Furthermore, the need for repeated epidural catheter insertion for recurrent painful events may raise concerns regarding feasibility. Finally, drug shortages may also affect delivery of the intervention. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepro.org/profile/b955e360a93d1c73908ba3f4548bc944>.

No recommendation: IV fluids for acute pain

SUMMARY OF THE EVIDENCE. Although the panel recognized that there is published literature⁶⁰ recommending IV fluid administration for the acute management of pain in patients with SCD and that this is a widespread practice,⁶¹ a systematic review identified no studies that addressed this question in the direct literature in patients with SCD.⁶² Given the etiology of acute pain in SCD (eg, acute erythrocyte sickling, rigidity, adhesion, and vasoocclusion, resulting in tissue ischemia and inflammation) and the proposed theory that providing IV fluids during acute pain improves the rheological properties of sickled erythrocytes, the panel determined that indirect evidence would not be applicable. Therefore, no searches were made for indirect evidence. Based on these considerations, the panel felt that any recommendation would be speculative, and therefore, they could not recommend for or against IV fluids for the treatment of acute pain.

BENEFITS. Without specific evidence to judge, the panel agreed that potential benefits of IV fluids could include improved pain intensity, shorter length of stay, decreased hospitalization and ED rates, and decreased opioid use. This therapy is available in all acute care settings, and the costs to deliver it are moderate.

HARMS AND BURDEN. The panel discussed the potential harm of administering bolus and/or maintenance IV fluids to patients with SCD presenting with acute pain and also the type of fluids that are administered in these infusions (eg, lactated Ringer's solution, normal [0.9%] saline, half-normal [0.45%] saline). The panel noted that these patients may also have underlying renal dysfunction and may be receiving nephrotoxic treatments (eg, NSAIDs) for their pain and/or cardiac dysfunction. It is possible that the risk of harm from IV fluid administration may be higher in adults than children, considering that adults with SCD have more comorbid conditions and cardiopulmonary dysfunction than children.

RATIONALE. Because systematic review did not identify any existing literature for the outcomes of interest in patients with SCD, the panel could not recommend for or against IV fluids for the acute treatment of pain. Any recommendation was felt to be speculative. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepro.org/profile/b955e360a93d1c73908ba3f4548bc944>.

CONCLUSIONS AND RESEARCH NEEDS (IV FLUIDS FOR ACUTE PAIN). The panel determined that studies investigating the impact of IV fluids (both in type and amount) for the treatment of acute pain in patients with SCD are needed. This is especially important considering that IV fluids are widely available and provided, have the potential to improve pain at a moderate cost, and are valued by patients as a therapy that can be used in addition to pharmacological treatment. However, they may also have significant risks, especially in this chronically ill population.

Conclusions and research needs (nonopioid pharmacological therapies for acute SCD pain).

The panel identified the following additional areas of research that are needed: (1) delineating nonopioid pharmacological interventions that most robustly affect care and improve outcomes, including multimodal combination therapies; (2) integrating the patient voice into research; there is a need to assess the impact of these interventions on patient-reported outcomes, satisfaction with care, and patient values and preferences; (3) developing new definitions of acute and chronic pain specific to SCD to improve study design and potential of a successful trial; (4) conducting formal cost-effectiveness studies to evaluate the economic impact of nonopioid interventions; these should be updated for evolving costs, take a broader system-level view, and incorporate both patient and societal costs, including long-term chronic complications associated with the interventions; and (5) conducting comparative-effectiveness research that reduces risk of bias.

Nonpharmacological therapies for acute SCD pain

Should nonpharmacological therapies in addition to pharmacological therapies be used for the treatment of acute pain in children and adults with SCD?

Recommendation 3

For *adults and children* who seek treatment of acute pain, the ASH guideline panel *suggests* massage, yoga, TENS, VR, and guided AV relaxation in addition to standard pharmacological management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based on direct evidence from patients with SCD and indirect evidence largely from postoperative adult mixed surgical populations.
- Despite the evidence being primarily based on adult populations, there is low risk of harm in children. However, a tailored approach should be used that matches feasibility and acceptability for a given patient. Some interventions may not apply to younger children; therefore, the age of the patient should be considered, especially for interventions such as yoga and guided AV relaxation.
- Time requirements, financial costs, availability, and training of therapists for these types of treatments are important factors in treatment selection and should be discussed with patients in the course of shared decision making.

No recommendation

For *adults and children* who seek treatment of acute pain, the ASH guideline panel chooses not to offer a recommendation for or against acupuncture or biofeedback for the treatment of acute pain in addition to standard pharmacological management.

Remarks:

- If biofeedback and acupuncture are considered, a tailored approach is necessary that matches feasibility,

acceptability, and patient experience and preference regarding these interventions for a given patient.

- Discussion with patients in the course of shared decision making needs to include important factors such as the time, financial costs, availability, and training of the therapists required to perform these treatments.

Specific background. A clinical hallmark of SCD is recurrent episodes of acute pain. The first line of treatment of SCD pain is pharmacological therapies, such as NSAIDs and opioids. However, medications alone have not been effective in relieving the burden and associated psychosocial consequences of acute pain in children and adults with SCD, and they have the potential for harmful adverse effects. Nonpharmacological interventions, such as massage, yoga, TENS, VR, guided AV relaxation, acupuncture, biofeedback, mindfulness, spirituality, CBT, and meditation, have the potential to ease pain and reduce the need for opioids or other pharmacological treatments, are accepted by patients with SCD, and may already be widely used for patients presenting in acute pain. Therefore, the panel sought to systematically review the existing data and appraise the evidence to determine whether nonpharmacological therapies should be used in addition to standard treatments (eg, opioids and NSAIDs) for the management of acute pain in SCD. Particular attention was paid to the impact of nonpharmacological therapies on patient-centered outcomes, including improved pain intensity, pain coping strategies, and HRQOL, reduction in total MME consumed and length of stay, and return to baseline pain.

Recommendation 3: massage, yoga, TENS, guided AV relaxation, and VR for treatment of acute pain

SUMMARY OF THE EVIDENCE. The systematic review identified 9 studies that addressed this broader question of nonpharmacological therapies for acute pain control in the direct literature in children and adults with SCD.⁶³⁻⁷⁰ Of these, there were 5 small RCTs, 1 small quasiexperimental interrupted time series study, and 1 feasibility study using massage,⁶⁷ yoga,⁶³ TENS,⁶⁵ guided imagery/AV relaxation,^{68,69} and VR⁷¹ in children or adults with SCD for the management of acute pain. Evidence ranged from low to high certainty for the following outcomes for these nonpharmacological interventions: (1) pain intensity: significant reduction in pain rating (yoga, TENS, massage, guided AV relaxation/imagery, VR); (2) analgesic intake or use: nonsignificant decrease in MME consumed (yoga, TENS, guided AV relaxation/imagery); (3) length of stay: no clear change (yoga, massage); and (4) pain coping: significant improvement in current stress levels (guided AV relaxation) but no significant change in average stress levels (guided AV relaxation). None of these studies reported on the frequency of hospitalizations or ED visits, HRQOL, or return to baseline pain. Because of the limited amount of direct evidence, the panel reviewed the indirect evidence to evaluate the impact of nonpharmacological interventions for the acute management of pain in mixed surgical populations. There were 7 systematic reviews identified in primarily mixed surgical populations using virtual reality,⁷²⁻⁷⁵ massage,⁷⁶ and TENS.^{77,78} These reviews found significant improvements in pain intensity (massage, TENS, and VR) and significant reductions in opioid use (TENS) and length of stay (TENS). Because direct evidence was primarily from small RCTs, and because there was a high degree of heterogeneity in the included indirect evidence that was reviewed, the recommendation

was downgraded to conditional based on the certainty in the evidence that was identified.

BENEFITS. The potential benefits of acute pain treatment with massage, yoga, TENS, guided AV relaxation/imagery, and VR are small and include improved pain control, pain coping, decreased opioid use, and decreased length of stay. Although the evidence was primarily based on adult populations, the panel agreed that there was low risk of harm in children. The panel also agreed that most patients value additional improved pain outcomes from these nonpharmacological therapies, especially considering that interventions such as yoga and massage likely have lower risks than conventional pharmacological treatments.

HARMS AND BURDEN. The panel discussed the fact that massage, yoga, TENS, guided AV relaxation/imagery, and VR have low risks of harm. Specifically, the panel discussed the potential for a paradoxical increase in pain perception with these interventions and the risk of harm if these interventions were improperly delivered. Also, the panel discussed the facts that for these interventions to be effective and to minimize these risks, a significant time and personnel commitment would be required to deliver these therapies and that patients would need to be motivated, able, and developmentally capable of participating in these therapies. Finally, the panel discussed the fact that moderate costs would be required to deliver these therapies.

RATIONALE AND KEY DRIVERS FOR RECOMMENDATION. The panel acknowledges that the evidence for use of these therapies in SCD is limited but also acknowledges that patients with SCD value nonpharmacological treatments that have few undesirable effects and can be used in conjunction with standard pharmacological treatments to reduce the burden of acute pain. Although there are moderate costs associated with delivering these interventions, the panel agreed that patients could also eventually be trained to self-administer some nonpharmacological interventions over time, and this may reduce the costs to deliver these interventions. Overall, the panel determined that the balance of effects favored the intervention. Because there were only small randomized studies in SCD patients and heterogeneous studies in the mixed surgical populations for these nonpharmacological interventions for management of acute pain, this led to downgrading the recommendation to conditional. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradeapro.org/profile/2e656cb3a285c52d2615120acbf1af4a>.

OTHER ETD CRITERIA AND CONSIDERATIONS. The guideline panel acknowledges that the systematic review did not identify data on all of the existing nonpharmacological therapies (eg, mindfulness, spirituality, exercise, and cognitive therapy) that may have the potential to reduce acute pain in SCD. The panel also discussed the fact that despite supportive evidence for use of some of these therapies, it may not be feasible to deliver some of these therapies in all acute care settings (eg, yoga in the ED). The panel felt that there was low certainty in evidence of the resources required to implement these interventions but that there was no important uncertainty or variability about how much patients value the main outcomes that were considered and that the cost effectiveness probably favored use of these interventions. The panel concluded that these interventions would be acceptable to patients in addition to standard pharmacological therapy.

CONCLUSIONS. The guideline panel determined that there is overall very low certainty in the evidence for a net benefit of massage, yoga, TENS, VR, and guided AV relaxation to reduce the burden and psychosocial impact of acute pain in patients with SCD. Despite the absence of large randomized studies that include pediatric and adult populations of patients with SCD, this recommendation is justified based on the value that patients place on nonpharmacological therapies that can be used in addition to standard pharmacological therapies, the low risk of harm, and the moderate costs associated with providing these interventions.

No recommendation: acupuncture and biofeedback for treatment of acute pain

SUMMARY OF THE EVIDENCE. Only 3 studies identified focused on acupuncture and biofeedback approaches for the treatment of acute pain in SCD.^{64,66,70} There were 2 small observational (pre-post) studies of acupuncture in adults (with age ranges of 18-39 and 19-67 years)^{64,66} and 1 small observational study of biofeedback in adults (age range, 22-35 years).⁷⁰ Evidence with low to very low certainty for the following outcomes existed: (1) length of stay: nonsignificant reduction in length of stay (biofeedback); (2) frequency of hospitalizations and ED visits: nonsignificant reduction in hospitalizations (biofeedback); (3) analgesic use: nonsignificant reduction in analgesic use (biofeedback); and (4) pain intensity: conflicting findings, with 1 study showing nonsignificant pain reduction and the other study showing significant pain reduction (acupuncture). These studies did not report on outcomes of pain coping, HRQOL, or return to baseline pain. Because of the lack of direct evidence on biofeedback and acupuncture for acute pain in SCD, the panel reviewed indirect evidence for these interventions for the acute management of pain in mixed surgical populations. One systematic review in mixed surgical populations using acupuncture, electroacupuncture, and transcutaneous electrical acupoint stimulation was identified.⁷⁹ This review found a statistically significant improvement in pain intensity and a nonsignificant reduction in opioid use. However, all of these systematic reviews cited insufficient methodological rigor of the trials that were included, and there were no studies testing these therapies in pediatric patients in acute pain.

BENEFITS. There was only speculative direct evidence supporting acupuncture use in adults with SCD and indirect evidence in adult mixed surgical populations on the benefits of acupuncture to reduce pain intensity. There was no direct or indirect evidence supporting the idea that biofeedback has benefits for the outcomes of interest.

HARMS AND BURDEN. The panel discussed the idea that acupuncture and biofeedback therapies have low risk of harm; however, improper delivery may increase this risk. Also, to benefit and minimize the potential risk of harm, significant time and personnel commitment are required to effectively and safely deliver acupuncture and biofeedback, and patients must be motivated and able to participate in these therapies. Finally, there are financial costs to deliver these therapies to patients.

RATIONALE AND CONCLUSIONS. The panel identified only very low-certainty direct evidence in adults with SCD and mixed surgical populations. Because of the speculative nature of the direct evidence and indirect evidence in adults from mixed surgical populations, a recommendation for or against the use of acupuncture or

biofeedback in addition to standard pharmacological treatment of acute pain could not be made.

Research needs. The panel identified the following additional areas of research that are needed: (1) delineating the impact that these therapies have on patients in acute pain, because few nonpharmacological therapies have been rigorously evaluated in patients with SCD; (2) evaluating the impact that these nonpharmacological approaches have on important patient-reported health outcomes, such as HRQOL or return to baseline pain; (3) determining if nonpharmacological approaches may be effective for the prevention of acute pain in SCD, the treatment of acute pain when it occurs, and the prevention of the development of chronic pain; and (4) developing protocols that operationalize the delivery of these therapies in the hospital and ambulatory settings.

Pain management in an SCD-specific hospital-based acute care facility

Should a hospital-based entity such as a day hospital or observation unit compared with regular ED care be used for children and adults with SCD who seek treatment of acute pain?

Recommendation 4

For *adults and children* who develop acute pain episodes requiring hospital care, the ASH guideline panel *suggests* using SCD-specific hospital-based acute care facilities (ie, day hospitals and infusion centers, all with appropriate expertise to evaluate, diagnose, and treat pain and other SCD complications) over typical ED-based care (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- This recommendation assumes that these hospital-based facilities have readily available code team coverage to ensure delivery of the safest care.
- From a hospital or system perspective, more detailed cost analyses would be warranted before deciding on implementation for a given institution. SCD-specific hospital-based acute care facilities tend to be cost effective to the extent that they reduce ED visits and admissions; however, overall acute care utilization may increase.
- Most of the evidence describing hospital-based acute care facilities places pain treatment in the context of complex SCD comprehensive care models. In these models, >1 intervention is likely driving the improvement and continuity in care.

Specific background. Children and adults with SCD have episodes of recurrent acute pain that result in the use of acute care facilities. Acute care for patients with SCD is most frequently provided in the ED. Treatment of pain in the ED is associated with barriers that affect care. These include lack of continuity and connection with the patient's SCD treatment team; delays in initial analgesic delivery, reassessments, and repeat dosing; stigma, discrimination, and negative provider attitudes, where patients are labeled as drug seeking, all of which could be magnified during the

current opioid epidemic; and increased costs to the patient and health care system. Therefore, many institutions have developed alternative models of care for acute pain that include delivery of pain management in a treatment center outside of the ED such as in a day hospital, observation unit, or infusion center. These alternative care delivery models allow patients direct access to pain management in the context of a specific facility where there is also continuity of care with their primary SCD health care team. The panel systematically reviewed and appraised the available evidence to determine how these alternative care delivery models compare with traditional ED care for the management of acute pain. Particular attention was paid to the impact on patient-centered outcomes including time to first analgesic dose, time between analgesic doses, improved pain intensity, need for subsequent ED care or hospitalization, missed days of school or work, HRQOL, and patient satisfaction with care and cost.

Summary of the evidence. The systematic review identified 9 studies⁸⁰⁻⁸⁸ that addressed this question from the direct literature in patients with SCD. Among these studies, there were 5 comparative observational studies, 2 noncomparative retrospective observational studies, and 2 pre-post observational studies. Evidence for the following outcomes existed: (1) hospitalization and ED visit rates: decreased need for hospital admissions with a non-ED treatment center (very low to intermediate certainty); (2) pain: overall decrease in pain intensity with non-ED treatment center (low to intermediate certainty); (3) time to initiation of analgesic therapy: decreased time to first dose of opioid with a non-ED treatment center (low to intermediate certainty); (4) length of stay: shorter duration of stay in the non-ED treatment center (low certainty); (5) need for ED care after discharge: lower rate of ED visits within 48 hours from discharge from a non-ED treatment center (low certainty); and (6) cost: overall decreased cost with a non-ED treatment center (low to intermediate certainty). There were no studies identified that addressed many of the a priori–defined patient-centered outcomes, including HRQOL, satisfaction with care, and missed days of school or work. Furthermore, minimal published data exist on hospital-based facilities that are off site from the main hospital campus. Because only observational data exist, and there was a lack of studies with experimental designs, the recommendation was downgraded to conditional based on very low, low, and intermediate certainty in the evidence about effects.

Benefits. The potential benefits of acute pain treatment in an SCD-specific hospital-based acute care facility (ie, day hospital, infusion center) are moderate and include improved pain control, shorter time to initiation of analgesic delivery, shorter length of stay, decreased hospitalization rates, decreased need for ED care after discharge from facility, and lower cost.

Harms and burden. The panel discussed the idea that the setting of the non-ED treatment center could determine the likelihood of undesirable effects. Specifically, there is a potential risk of other medical complications and clinical instability that may arise during the treatment of pain that requires resuscitative care. The management of these complications would be best served in a facility that has prompt access to a higher level of care, such as the ED. Therefore, free-standing sites that are not hospital based may be disadvantaged in this regard and could pose a safety concern. Published data on the use of free-standing and off-site centers are lacking. Therefore, the panel carefully defined a non-ED

treatment center as an SCD-specific hospital-based acute care facility (ie, day hospital, infusions center). The key driver of this definition is hospital based to ensure access to higher levels of care if needed to minimize harms.

Rationale and key driver for recommendation. The balance of benefits vs harms favors the intervention. The panel identified few undesirable effects of the intervention except for the resources that are required to set up and maintain these facilities. The panel felt strongly that hospital-based acute care facilities were preferable and important (vs free-standing, off-site facilities). These sites should have ready access to the main ED or other areas of the hospital with acute care expertise (eg, intensive care unit) in case of an acute need for a higher level of care. Overall, the balance of effects favored the intervention. As noted, there were only observational data and a lack of data derived from experimental designs, which led to the downgrading of the recommendation to conditional. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepr.org/profile/11b0b2910435f2e635bb28bd6abd8247>.

Other EtD criteria and considerations. The most relevant and informative term to define these non-ED treatment centers was discussed extensively (eg, day hospital, infusion clinic, acute pain center). The panel determined that for accreditation issues, there could be a preference for infusion center or day hospital as the most relevant term. For the recommendation, the panel settled on the general term of SCD-specific hospital-based acute care facility (ie, day hospitals, infusion centers, and observation units, all with appropriate expertise to treat pain). The panel acknowledged that there was no important uncertainty or variability about how much people value the main outcomes that were considered. Patients place importance on timely pain management and an accessible place to access care for analgesia and admission, if needed. Avoiding ED visits is preferable when possible.

The panel also considered resource requirements for implementation of the SCD-specific acute care facility. The panel discussed the fact that costs and resources can depend on the number of patients expected to use the SCD-specific acute care facility for pain management. The cost savings are likely largely due to reduced ED use, admissions, and readmissions. The panel acknowledged that there was likely low certainty of the evidence of resource requirements. An SCD-specific hospital-based acute care facility care is less costly than ED care on a per-patient basis. However, the assessment of savings will depend on the volume of patients in the center. Several other contextual variations can influence cost, including the hours of operation. The panel discussed the idea that the cost effectiveness may be hard to fully understand, because the savings from reduced hospitalizations may be offset by increased acute care utilization in the SCD-specific hospital-based acute care facility because of more rapid treatment and reduced stigma. There is a lack of data on what the actual savings are when balancing acute care utilization and SCD-specific hospital-based acute care facility use. The panel concluded that the cost effectiveness of the intervention probably favors the intervention. The panel felt that an isolated/free-standing SCD care center is unlikely to be cost effective.

The panel felt that SCD-specific hospital-based acute care facility care would increase health equity, because care would be easier to access, the admission process (if needed) would often be

expedited, and there would be overall reduced waiting time. Equity was also felt to be potentially increased with the SCD-specific hospital-based acute care facility model, because there may be prompter return to work after treatment as a result of more rapid treatment. The panel did raise a few concerns about how SCD-specific hospital-based acute care facility models could reduce health equity. These included the geographical location of these facilities and the fact that ED access may be easier in some circumstances if patients arrive via emergency medical services. Transportation to and from an SCD-specific hospital-based acute care facility may be more difficult for patients without access to private vehicles. The panel acknowledges that there is a lack of research on patient preferences for this intervention that could inform health equity. In balancing all issues discussed, the panel felt the overall impact would be an increase in health equity.

The panel concluded that the intervention would be acceptable to key stakeholders. The panel felt that patients would prefer the familiar caregivers and reduced wait times that an SCD-specific hospital-based acute care facility model provides. The panel also discussed the idea that the ED staff would also likely prefer that patients access the SCD-specific hospital-based acute care facility for pain management to optimize continuity of care. Finally, the panel acknowledges that the feasibility of implementation of SCD-specific hospital-based acute care facilities for pain treatment varies. The panel discussed the fact that justification for the SCD-specific hospital-based acute care facility model for pain management depends on a sufficient critical mass of patients. An SCD-specific hospital-based acute care facility may be justifiable if costs are lower and if it can offload ED care. Furthermore, SCD-specific hospital-based acute care facilities can have other functions and serve multiple purposes. The panel also discussed specific implementation considerations that include potential safety concerns for facilities that are off site from a hospital. The panel felt that optimal implementation occurs when there seems to be positive bidirectional practice between the SCD-specific hospital-based acute care facility and the ED. This requires a proactive approach to ensure that bidirectional communication occurs. There may be financial pressures that create competition for appointments in a general day hospital center that is not solely for patients with SCD and limits their access to emergency appointments.

Conclusions and research needs. The panel acknowledges that pain treatment using these SCD-specific hospital-based acute care facilities could be multifaceted interventions that include more than just analgesic delivery. The additional aspects of the intervention are likely important, and the site of care (ED vs non-ED treatment center) may not be the only driving factor that positively affects the outcomes. The independent impact of the site of care separate from other aspects of the care delivery model is difficult to assess.

The panel identified the following areas of research that are needed: (1) delineate aspects of the intervention that most robustly affect care and improve outcomes; many studies include multifaceted interventions for non-ED based care that are often part of a larger comprehensive SCD care model; (2) integrate the patient voice into research; there is a need to assess the impact of these care delivery models on patient-reported outcomes, satisfaction with care, and patient values and preferences; (3) investigate protocols to operationalize personalized treatment in SCD-specific hospital-based acute

care facilities; (4) assess integration and efficacy of other nonopioid and nonpharmacological pain treatments in these care delivery models; (5) compare utilization patterns in systems that rely on ED-based care and those that rely on SCD-specific hospital-based acute care facilities; in addition, studies that assess long-term outcomes linked to SCD-specific hospital-based acute care facilities compared with traditional ED-based care are needed; (6) carry out more formal cost-effectiveness studies to evaluate the economic impact of SCD-specific hospital-based acute care facilities; these should be updated for evolving costs and take a broader system-level view and incorporate both patient and societal costs; and (7) conduct comparative research to reduce the risk of bias. As a matter of policy, the panel agreed that the development of infrastructure and funding models to support such interventions and investigations into their efficacy and effectiveness is needed. Furthermore, there is a need for research into system barriers and solutions to these barriers to provide the evidence base that can facilitate successful implementation of this recommendation.

Continuous basal opioid infusion for acute SCD pain treatment

Should a combination of continuous basal opioid infusion with on-demand dosing vs on-demand opioid dosing alone or scheduled intermittent opioid dosing be used for children and adults with SCD hospitalized for the treatment of acute pain?

No recommendation

For children and adults with SCD who seek treatment of acute pain in the hospital, the ASH guideline panel chooses not to offer a recommendation for or against basal opioid dosing in conjunction with on-demand dosing or scheduled intermittent dosing.

Remarks:

For clarity, the panel defined the specific terms used as follows:

- Basal: continuous IV opioid infusion.
- On-demand dosing: opioid administered at an interval that relies on patients declaring their own need. Opioid can be administered via a patient-controlled IV analgesia pump or via an as-needed order for intermittent nurse-administered drug.
- Scheduled intermittent dosing: opioid administered on a timed schedule that does not rely on the patient asking for the drug.

Specific background. Children and adults living with SCD require hospitalization for acute pain management. The standard of care at most institutions is to deliver IV opioids via PCA when appropriate. The addition of a basal (ie, continuous) IV opioid infusion to the on-demand dosing schedule via PCA is a widespread practice. The panel acknowledges that opioid delivery via PCA offers clear advantages over alternative drug delivery strategies. However, what is less clear is whether the addition of a continuous basal opioid infusion to intermittent opioid delivery offers advantages considering the balance of benefits and harms over intermittent opioid delivery alone. Clear guidelines for treatment of acute pain in individuals living with SCD do not currently exist for opioid delivery in this manner that balance benefits and risks/harms. A systematic

review of pediatric and adult data and appraisal of the evidence were conducted to inform this question and recommendation.

Summary of the evidence. The systematic review did not identify any direct evidence in individuals living with SCD that informed this question. There was a preliminary report of 1 RCT conducted in children and adults with SCD, which was terminated early because of low accrual, that intended to compare different approaches of opioid administration via PCA in the 2 study arms (ie, higher-demand dose with low constant infusion vs lower-demand dose and higher constant infusion).⁸⁹ However, this study did not directly inform this question, because all patients in the RCT received a basal opioid infusion. Therefore, this study was not included in the final evidence profile pertaining to this question. Because there was an absence of direct evidence, the panel agreed to search the indirect evidence. The indirect evidence review focused only on published systematic reviews and meta-analyses that addressed the use of benefits or harms of basal opioid infusions for pain in pediatric and adult populations. This review identified 2 studies for inclusion.^{90,91} One meta-analysis included adults and children of mixed postoperative patient populations.⁹⁰ This study analyzed 14 articles that encompassed 402 participants in the basal opioid infusion group plus on-demand PCA and 394 participants in the on-demand opioid via PCA group. This study was focused only on the harm of respiratory depression and did not analyze data for efficacy/effectiveness. Results support some concern for increased risk of respiratory depression associated with basal infusions in adult but not pediatric patient populations. However, these data were limited by the lack of a uniform definition of respiratory depression across studies, and this definition included a decrease in respiratory rate, drop in oxygen saturation, or overt somnolence, which led the authors to use a guideline-based definition⁹² to analyze the data. Other limitations included the small sample size, nonuniform opioid dosing, and specific opioid administered across studies. The authors concluded from this study that their results could not be used to determine overall safety of a continuous opioid infusion. The authors suggested that these data not be used for specific treatment recommendations and that the addition of a basal infusion to on-demand opioid PCA may be appropriate for opioid-tolerant patients (such as in SCD). Another systematic review and meta-analysis focused on postoperative pain in children only.⁹¹ This study analyzed 7 articles that encompassed 338 participants. Five of the studies included 12- and 24-hour pain intensity scores in the basal opioid infusion plus on-demand PCA group ($n = 108$) and in the on-demand opioid via PCA group ($n = 95$). This study was focused only on the harm. No difference in efficacy/effectiveness was identified in this small sample. Basal plus on-demand dosing ($n = 174$) did not differ from on-demand dosing alone ($n = 164$) in total opioid consumption. There were no differences in harm (nausea/vomiting or excessive sedation) in 4 studies reporting these variables. These authors did not suggest clinical action be taken regarding these data, because the sample size was very small and likely unpowered. After discussing the indirect evidence, the panel concluded that because this evidence consisted primarily of opioid-naïve and postoperative patients, it was less relevant to patients with SCD who are likely to be opioid tolerant after a cumulative exposure to opioids over their lifespan. Therefore, the panel did not have evidence on which to base a recommendation and put forth a nonrecommendation for this question.

Benefits. There was no direct evidence identified that addressed the desirable effects of continuous basal opioid infusion in individuals living with SCD and hospitalized for the treatment of acute pain. Furthermore, the panel concluded that the indirect evidence was likely not applicable to all individuals with SCD, because it included patients who were likely to be opioid naïve and postoperative. Therefore, the panel concluded that the true benefit of basal opioid infusion in addition to on-demand opioids as a treatment of acute SCD pain is largely unknown.

Harms and burden. The systematic review did not identify any direct evidence addressing the harms of continuous basal opioid infusion in children and adults living with SCD. Therefore, the harms of this treatment in patients with SCD are incompletely understood because of the lack of evidence. Indirect evidence was searched to attempt to assess risk of harm associated with the use of basal continuous opioid infusions in addition to on-demand opioid PCA. The indirect evidence reviewed above suggests an increased risk of respiratory depression; however, these data are subject to the methodological issues outlined above and were derived primarily from postoperative surgical patients who were likely opioid naïve, making the data less relevant to individuals living with SCD, who are often opioid tolerant or are not recovering from an anesthetic or surgical procedure.

Rationale. Although the panel recognizes the addition of basal opioid dosing to be a widespread practice, direct evidence to support a recommendation was not identified. Furthermore, the indirect evidence consists primarily of opioid-naïve and postoperative patients and is likely less relevant to individuals living with SCD. Therefore, the panel concluded that any recommendation for this question would be too speculative. Although there is a potential risk for harm in patients as outlined above, the panel concluded that because these data were derived from patients who were likely to be opioid naïve to a greater extent than individuals with SCD, the evidence was too indirect and speculative, limiting the ability to extrapolate to patients with SCD. The panel did discuss the fact that the theoretical risk for harm could differ between pediatric and adult patients with SCD because of other comorbidities that may independently increase the risk for harm (eg, obesity, sleep apnea, chronic lung disease, hepatic dysfunction, and renal insufficiency). Therefore, clinician assessment on an individual basis should be used for a given patient while balancing the potential risk for harm and absence of data that address benefit. Ultimately, because the risk for harm has not been studied in patients with SCD, who are often not opioid naïve, and no studies have investigated the benefit, a recommendation in either direction could not be made. Therefore, the panel concluded that in the absence of data, the balance of benefits vs harms could not be established and has put forth a nonrecommendation for this question. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepr.org/profile/756565264e01ad84088def689f071af0>.

Other EtD criteria and considerations. The panel acknowledges that there was no important uncertainty or variability about how much people value the main outcomes that were considered. Patients place significant importance on pain relief and improved functioning with the fewest adverse effects and risks for harm. The panel, including the patient representatives, determined that there is an important need to engage patients in a discussion about the

use of basal opioid infusions in addition to on-demand opioid via PCA before initiation. This should include a discussion of the theoretical risks of basal opioid infusion and the absence of evidence that addresses the benefits. However, there is a lack of published data that address values and preferences regarding basal opioid infusions specifically in individuals with SCD. The panel acknowledges that individuals treated with basal opioid infusions require frequent monitoring, which likely has associated financial costs; however, no data exist to assess these costs. There is a lack of data that address differences in length of stay with or without basal opioid infusion and the effect of this intervention on patient-reported outcomes; both of these topics were identified as research gaps. The panel acknowledges that hospital policy may affect the ability of the provider to use basal opioid infusions in addition to on-demand opioid PCA, because these policies are not patient population specific and do not differentiate opioid-naïve from opioid-tolerant patients. These policies could have a negative impact on health equity if a patient receives a benefit with a basal opioid infusion and has no concerns for harm. The panel also acknowledges that the acceptability of basal opioid infusions likely varies based on the individual patient, family, provider, and institution, and there is an absence of data to inform this issue.

Conclusions and research needs. Because of the absence of data addressing the efficacy, effectiveness, and harms of basal opioid infusions in addition to on-demand opioid treatment in individuals with SCD and the inability of the panel to make a recommendation, the panel discussed the following research priorities for children, adolescents, and adults living with SCD: (1) study benefits and harms associated with basal opioid infusions in children, adolescents, and adults with inclusion of patient-reported outcomes and length of stay as patient-centered end points; (2) comparative-effectiveness research with existing data to determine benefits and harms of basal opioid infusions; and (3) safety registries to monitor adverse events in hospitals that administer basal opioid infusions in addition to on-demand opioid PCA strategies.

Nonopioid pharmacological therapies for chronic pain in SCD with another identifiable cause

Should nonopioid pharmacological therapy, either in addition to or instead of opioids or other usual care interventions, be used for children and adults with SCD and chronic pain with another identifiable cause (eg, avascular necrosis, leg ulcers)?

Introduction. The ASH guideline panel suggests an individualized approach to initiating or discontinuing nonopioid therapy that is based on the balance between benefits and risks/harms and should consider functional outcomes and the durability of benefit over time. The panel's recommendations are divided into 2 defined medication groups and are based on the clear presence of chronic (rather than episodic) pain.

Recommendation 6a

For *adults* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel *suggests* use of duloxetine (and other SNRI medications, because there is evidence of a class effect) as an option for management, in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Recommendation 6b

For *adults* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel *suggests* the use of NSAIDs as an option for management, in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

No recommendation

For *children* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of avascular necrosis of bone, the ASH guideline panel chooses not to offer a recommendation for or against the use of SNRIs and/or NSAIDs.

No recommendation

For *adults and children* with SCD who have chronic (as opposed to episodic) pain from the SCD-related identifiable cause of leg ulcers, the ASH guideline panel chooses not to offer a recommendation for or against any specific nonopioid pharmacological management strategy.

Remarks:

- NSAIDs herein are defined broadly to include selective and nonselective COX inhibitors.
- There was a lack of both direct and indirect evidence for all-cause avascular necrosis nonsurgical pain management. Therefore, the panel chose to use osteoarthritis as an indirect evidence source, because it is a degenerative arthropathy with a reasonable evidence base. This evidence base was restricted to adults.
- Surgical and nonsurgical approaches to the treatment of the underlying cause of avascular necrosis were not the focus of this recommendation.

Good practice statement

It is good practice to provide patient-centered education and surveillance related to NSAID toxicity, especially in patients with end-organ comorbidities, because long-term safety data are lacking for SCD, but vascular, bleeding, and renal risks may be elevated.

Good practice statement

Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Specific background. Noncrisis and chronic pain are common in patients with SCD, particularly among adults. For adults, the prevalence of near-daily pain is estimated at >25% and that of pain most days as >50%.² Current evidence also suggests that those who have greater levels of chronic pain have associated increases in acute pain.² Although there is some evidence guiding strategies to prevent crisis pain and to treat it acutely in acute care settings, the treatment of noncrisis and chronic pain in SCD lacks a firm evidence base. Chronic pain in SCD often has no discernible associated pathology beyond the SCD itself; however, SCD is a risk factor for multiple complications that are themselves painful. Some

of these complications, including avascular necrosis of bone and leg ulcers, are either permanent or long lasting and likely become independent causes of chronic pain.^{93,94}

The panel sought to identify the most relevant painful complications of SCD that were independently associated with chronic pain and to systematically review the existing data and appraise the evidence to determine if it was sufficient to recommend any nonopioid pharmacological strategies to treat the pain associated with these conditions and, if so, which could be recommended. A priori, the panel sought evidence of effects on chronic pain intensity/severity, pain interference, and function. However, direct evidence addressing these outcomes was absent.

Summary of the evidence. The systematic review of direct evidence identified only 3 studies that might address the question in patients with SCD. However, these studies were judged to be inadequate to guide recommendations. One study of methotrexate for crisis pain reported reductions in chronic avascular necrosis pain as a secondary outcome, but this outcome was inadequately described, and the study was not designed to address chronic pain.⁹⁵ Another small study investigated sodium salicylate iontophoresis as an add-on to conventional physical therapy and medications and was limited by small sample size, rigor of methods, and limited descriptions of the control vs intervention groups.⁹⁶ The 1 study identified as possible direct evidence for leg ulcers was a case series reporting outcomes of subcutaneous calcium heparin plus human antithrombin concentrate in adults with sickle cell β thalassemia, which addressed wound healing rather than pain.⁹⁷

Lacking adequate direct evidence, the panel turned to indirect evidence to formulate recommendations. The indirect evidence base for leg ulcers largely was drawn from diabetic leg ulcers, and the literature was focused on wound healing outcomes rather than symptomatic treatment of pain. Therefore, the panel agreed that the evidence base was too indirect to form a recommendation for pain management of leg ulcers in SCD. With respect to avascular necrosis of bone, the panel reviewed the evidence base for symptomatic treatment of pain related to osteoarthritis, which is a degenerative arthropathy with a substantial evidence base. See discussion in "Methods" that addresses the iterative process used by the panel to reach consensus for pain populations in which to search for indirect evidence. Based on this review, the panel identified 2 nonopioid medications with sufficient evidence to warrant recommendations.

DULOXETINE. Two systematic reviews of the use of duloxetine for knee osteoarthritis were identified,^{98,99} and another for multiple agents for multijoint osteoarthritis including duloxetine was also found.¹⁰⁰ The most recent and inclusive systematic reviews of knee osteoarthritis examined 3 RCTs with >1000 participants enrolled and supported the efficacy and safety of oral duloxetine in doses ranging from 60 to 120 mg per day for knee osteoarthritis at 10 to 13 weeks of treatment.⁹⁹ Both pain intensity and functional outcomes were assessed. Effects on pain were modest, with a calculated mean difference in pain intensity of -0.88 (95% confidence interval [CI], -1.11 to -0.65). There was a statistically significant difference in the Western Ontario and McMaster Universities Arthritis Index (WOMAC), a composite outcome including subscales for pain, stiffness, and physical function, between duloxetine and control groups. The physical function WOMAC subscale also showed improvement with duloxetine over placebo (mean difference [MD], -4.25 ; 95% CI, -5.82 to -2.68 ; $P < .0001$).

Estimates of minimum clinically important differences for WOMAC scales have varied,¹⁰¹ but based on these estimates, overall clinical effects are likely to be quite modest. The multijoint, multi-intervention systematic review concluded that duloxetine is likely to have similar efficacy to other post-first-line pharmacotherapies for osteoarthritis.¹⁰⁰

COX-2 INHIBITORS. A systematic review of celecoxib, a selective COX-2 inhibitor, at a dose of 200 mg per day orally for osteoarthritis was identified.^{102,103} Fifteen placebo-controlled RCTs were included, including 3750 patients. Celecoxib demonstrated a statistically significant reduction in total WOMAC score (MD, -4.41 ; 95% CI, -7.27 to -1.55), the WOMAC pain scale (MD, -0.86 ; 95% CI, -1.10 to -0.62), and the WOMAC function subscale (MD, -2.90 ; 95% CI, -5.12 to -0.67). Celecoxib also demonstrated significantly more gastrointestinal adverse events than placebo in these trials.

One network meta-analysis of oral agents for knee osteoarthritis was also identified,¹⁰⁴ including between 16 230 and 9742 participants depending on outcome examined. Overall results supported the use of etoricoxib, naproxen, acetaminophen, and celecoxib for osteoarthritis pain, supporting a class effect for NSAIDs. Other systematic reviews of multijoint osteoarthritis identified subsequent to the initial evidence review support efficacy of NSAIDs,¹⁰⁵⁻¹⁰⁸ although the results overall suggested that acetaminophen's effects may not be clinically significant,^{106,107} and some studies have questioned how many of these results can be attributed to confounding factors rather than treatment effects.^{103,109} Other evidence suggests that topical NSAIDs have short-term effects but likely are inferior to systemic NSAIDs.¹¹⁰

Benefits. The potential benefits of both duloxetine (and likely other SNRI medications) and celecoxib (and likely other NSAIDs) for avascular necrosis of bone are estimated to be small and include improved pain control and improved physical function related to affected joints.

Harms and burden.

DULOXETINE AND OTHER SNRIs. Although SNRI treatment in general seems to be associated with few serious adverse events,⁹⁹ these drugs have not been systematically studied in people with SCD, and there may be unknown interactions with the primary disease process that alter risk. One particular concern may be sexual dysfunction, which is a common adverse effect of medications with serotonin reuptake inhibition and is also common in people with SCD. Men with SCD who have a history of priapism and/or erectile dysfunction may be particularly at risk, although again, this has not been systematically studied. When used to treat psychiatric conditions, antidepressant medications can increase suicidal ideation in those age <25 years.¹¹¹ Whether this is true when they are used for chronic pain is unknown, and the indirect evidence base addressed adults and often older adults. Therefore, because of the lack of both direct and indirect evidence in children, and the further lack of sufficient evidence to ascertain the risks of chronic treatment starting at a young age, the panel agreed that no recommendation could be made for the use of SNRIs in children.

NSAIDs (SELECTIVE AND NONSELECTIVE COX INHIBITORS). The panel discussed several concerns surrounding use of NSAIDs in SCD. The main areas of concern included bleeding risk, renal function, and cardiovascular risks. Exposure to nonselective COX and selective COX-2 inhibitors may increase the risk of renal disease

and stroke,¹¹²⁻¹¹⁵ both of which are prevalent in patients with SCD, particularly in adults. Patients may also be particularly at risk for gastrointestinal bleeding or resulting chronic iron deficiency impairing hematopoiesis.¹¹⁶ The risks of exposure to NSAIDs also are likely dose and duration dependent, although there may be some differences in risk between selective and nonselective COX inhibitors and possibly different medications within subclasses.²⁰ These risks must be weighed against the risks of nonintervention, surgical options, nonpharmacological options, opioid therapy, or combinations of these; however, all the previously noted risks are poorly defined in SCD, and so such a calculation is extremely difficult. Overall, the panel concluded that the known and unknown risks and benefits of all options should be discussed between patients and clinicians, and close attention should be paid to whether clinically significant improvements are achieved with trials of reasonable doses and durations to justify continuing, and possibly cumulative, risks. As for SNRIs, the indirect evidence base addressed only adults and mainly older adults, as expected from the epidemiology of osteoarthritis. There might be specific risks for treatment of children, including the cumulative risk of long exposures, that are relevant but unknown.

Rationale and key driver for recommendations. The panel agreed that there is reasonable evidence that duloxetine (and likely other SNRIs) and/or celecoxib (and likely other NSAIDs) are superior to placebo and nonintervention for pain and functional outcomes. Relative to the risks and modest benefits that usual nonoperative care for pain in avascular necrosis of bone offers, the panel concluded that there is reasonable evidence that there will be some patients with SCD and avascular necrosis of bone for which benefits of these interventions will outweigh risks. However, because of the reliance on indirect evidence base and minimal evidence of risk in patients with SCD, this recommendation was downgraded to conditional based on very low certainty in the evidence about effects. In addition, because of the lack of both direct and indirect evidence in children, and the further lack of sufficient evidence to ascertain the risks of chronic treatment starting at a young age, the panel agreed that no recommendation could be made for the use of NSAIDs in children. The panel identified further investigation of both efficacy and risks in this population, particularly for NSAIDs, as an important priority. In general, the panel attempted to address the management of pain for SCD-related leg ulcers. Most of the direct evidence addressed ulcer healing rather than symptomatic pain relief. Furthermore, indirect evidence involved conditions with more complex pain pathology (ie, diabetic leg ulcers) and mainly addressed wound healing. Therefore, no recommendation could be made for SCD-related leg ulcer pain management. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepr.org/profile/8e46c85e20dac54b2ae517395514db4e>.

Other EtD criteria and considerations. The guideline panel determined that there was no significant doubt that the problem of pain management in avascular necrosis and leg ulcers is a priority. However, there is no direct evidence for efficacy of pharmacological options for either of these conditions or any evidence to delineate whether the risks differ for patients with SCD and others, although there are good reasons to believe that they do. The interventions are quite feasible, and although costs likely are no greater than those of other pharmacotherapies and may be lower than those of

some interventional procedures, small effects in the indirect evidence base suggest that any cost savings likely will also be minimal.

Conclusions and research needs. Because of the absence of direct data addressing the efficacy, effectiveness, and harms of nonopioid pharmacological therapies for chronic SCD pain with an identifiable cause, the panel discussed the following research priorities for children, adolescents, and adults living with SCD: (1) conduct RCTs of these nonopioid pharmacological medications in individuals living with SCD to delineate their efficacy, effectiveness, and risks for chronic SCD pain as result of avascular necrosis, leg ulcers, and other etiologies with an identifiable cause, and (2) conduct large-scale observational studies to assess the risks/harms of NSAID use in patients with SCD.

Nonopioid pharmacological therapies for chronic pain in SCD and no identifiable cause beyond SCD

Should nonopioid pharmacological therapy, either in addition to or instead of opioids or other usual care interventions, be used for children and adults with SCD and chronic pain with no identifiable cause beyond SCD?

Introduction. The ASH guideline panel suggests an individualized approach to initiating or discontinuing nonopioid therapy that is based on the balance between benefits and risks/harms and should consider functional outcomes and the durability of benefit over time. The panel's recommendations are divided into 3 defined medication groups and are based on the clear presence of chronic (rather than episodic) pain.

Recommendation 7a

For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* SNRIs (eg, duloxetine and milnacipran) as options for pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD (with no identifiable cause beyond SCD).
- Antidepressants may increase the risk of suicidal ideation and behavior in children and adolescents with major depression disorder and other psychiatric disorders.
- The significant lack of pediatric data for the use of SNRIs for pain management could not support a recommendation for this age group.

Recommendation 7b

For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* TCAs (eg, amitriptyline) as an option for pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD with no identifiable cause.
- Antidepressants may increase the risk of suicidal ideation and behavior in children and adolescents with major depression disorder and other psychiatric disorders.
- The significant lack of pediatric data for the use of TCAs for pain management could not support a recommendation for this age group.
- The increased adverse effect profile for this drug includes, but is not limited to, prolonged QT, orthostasis, cognitive impairment, dry mouth, and anticholinergic effects. These adverse effects should be considered and discussed with patients.

Recommendation 7c

For *adults* who have SCD-related chronic pain with no identifiable cause beyond SCD, the ASH guideline panel *suggests* gabapentinoids (eg, pregabalin) as options for pain management (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- This recommendation is based largely on indirect evidence from adult patients without SCD affected with fibromyalgia. Fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD with no identifiable cause.
- The significant lack of pediatric data for the use of gabapentinoids for pain management could not support a recommendation for this age group.

Good practice statement

Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Specific background. Individuals living with SCD suffer from chronic pain. The prevalence of chronic pain increases with age and may not be associated with an identifiable cause (eg, avascular necrosis, leg ulcers). Chronic pain in individuals with SCD is often treated with opioid and nonopioid analgesic medications. There is currently a paucity of evidence-based guidelines comparing chronic nonopioid therapy with COT for chronic SCD pain. Therefore, a systematic review of existing data was conducted with an appraisal of the evidence for the effect of chronic nonopioid therapy on patient-important outcomes, including efficacy, effectiveness, and harms. Data reviewed included both pediatric and adult populations to inform this question and recommendation.

Summary of the evidence. There was minimal direct evidence identified that informed this question in patients with SCD. The

systematic review of direct evidence identified no studies comparing opioid with nonopioid analgesic medications in patients with chronic SCD pain. The systematic review of direct evidence identified only 2 RCTs comparing nonopioid analgesic medications with placebo in patients with chronic SCD pain.^{117,118} Osunkwo et al¹¹⁷ found no difference between vitamin D and placebo treatment of chronic pain in SCD in a small RCT (n = 39). Schlaeger et al¹¹⁸ conducted a small pilot RCT comparing pregabalin with placebo; however, the trial had a large dropout rate, resulting in findings that do not guide treatment options. One observational study of opioid and nonopioid analgesics in patients with SCD and chronic pain using a Medicaid database with a small cohort of 2194 patients was identified.¹¹⁹ This study found that children receiving a combination of opioid with a selective serotonin reuptake inhibitor or an opioid with an anticonvulsant had a decrease in the number of vasoocclusive episode visits to a clinician. Collectively, the direct evidence was judged to be inadequate to guide recommendations. Therefore, the panel agreed on the importance of searching the indirect evidence for pain populations other than SCD patients. An iterative process was conducted to reach consensus about pain populations that were most closely related to SCD patients with chronic pain without an identifiable cause beyond SCD. The chronic pain associated with SCD is often multifocal or widespread and associated with significant disability, loss of function, and diminished QOL. Therefore, fibromyalgia was selected by panel consensus as the entity most closely aligned with chronic pain in SCD (with no identifiable cause beyond SCD). The indirect evidence reviews focused only on published systematic reviews and meta-analyses that addressed the use of chronic nonopioid therapy for fibromyalgia in pediatric and adult populations. This review identified 14 publications that were included in the evidence profile, 5 of which were the most currently available Cochrane Database systematic reviews. All RCTs included in the systematic reviews/meta-analyses used a placebo comparator for the nonopioid analgesic; no study compared opioid with nonopioid analgesics. Of these 14 reviews, 1 addressed the use of nonopioid analgesic therapy in children and adolescents with fibromyalgia.¹²⁰ However, this review identified only a single study, and therefore, meta-analysis could not be performed. Evidence from the other 13 systematic reviews/meta-analyses in adults addressed the following outcomes: pain relief, functional outcomes, and adverse outcomes. Regarding pain relief and functional outcomes, a key point from the data synthesis was that to date, there is high-quality research allowing reliable conclusions about the efficacy or effectiveness of long-term chronic nonopioid therapy for fibromyalgia pain in adult populations but not pediatric populations. The evidence is summarized by drug class.

SNRIs. One review¹²¹ included 10 RCTs (n = 6038) and concluded that SNRIs (milnacipran and duloxetine) were associated with reduced pain compared with placebo on a 100-mm VAS used for pain assessment. Nine studies (n = 5656) were included and concluded that SNRIs reduced fatigue. Sleep disturbance resulting from pain and QOL were also improved by SNRIs.

TCAs. The TCA amitriptyline was found to improve pain intensity, function, QOL, and sleep in a systematic review/meta-analysis of 9 studies (n = 520).¹²²

GABAPENTINOIDS. A systematic review of the gabapentinoid pregabalin found in a meta-analysis of 5 RCTs (n = 1874)¹²³ a significant reduction in pain intensity and improvement in a measure of patients' global impression of benefit; however, no measures of physical

function were investigated. Patients in the treatment arm reported significantly more somnolence, dizziness, weight gain, and peripheral edema than those in the placebo arm. Ultimately, because only indirect data were available to address this question, all recommendations were downgraded to conditional based on very low certainty in the evidence about effects.

MEDICAL CANNABIS. The position of the panel was that it would be inappropriate to weigh in on the use of cannabis, a drug that is illegal in the United States of America at the federal level.

Benefits. There is a significant absence of data that address the desirable effects of chronic nonopioid therapy in individuals living with chronic pain associated with SCD without an identifiable cause. Therefore, all data reviewed were from published systematic reviews and meta-analyses conducted in another chronic noncancer pain population, those with fibromyalgia. Indirect data that discuss potential benefits identified and synthesized by the panel are outlined briefly above. There may be benefits of chronic nonopioid therapy with gabapentinoids, including pregabalin; SNRIs, including duloxetine and milnacipran; and TCAs, including amitriptyline, over opioid analgesics for pain relief in individuals with chronic SCD pain. However, data assessing the benefits of chronic nonopioid therapy compared with opioid analgesics were not found in a meta-analysis or systematic review. Notably, there is an absence of data assessing the benefits of chronic nonopioid therapy in children and adolescent populations. Therefore, the panel concluded that the benefits of chronic nonopioid therapy for individuals living with SCD and suffering from chronic pain are limited to adult populations and include the medications pregabalin, duloxetine, milnacipran, and amitriptyline, based on indirect evidence.

Harms and burden. Notably, the harms related to chronic nonopioid therapy in children and adolescents with SCD are largely unknown. The panel discussed the known risks of chronic nonopioid therapy that have been published in the indirect literature regarding adult patients in the chronic noncancer pain population of fibromyalgia patients. The panel concluded that the undesirable effects vary based on the intervention. These are outlined in more detail in each recommendation. In general, the panel concluded that the undesirable effects of the interventions addressed in the recommendations are not likely to be different in patients with SCD and in those with fibromyalgia. These drugs have established lists of contraindications, adverse effects, and patients who should not receive them. In patients receiving COT, the prescribing clinician should weigh risks and benefits of the inclusion of other medications with problematic interactions such as sedation, constipation, or respiratory suppression. These issues are not SCD specific but should be considered before prescribing the medication. A Cochrane systematic review that addressed nonopioid therapy for chronic noncancer pain in children and adolescents identified a single study¹²⁰ that addressed risks in adolescents. This study examined the use of pregabalin in adolescents with fibromyalgia and found no difference from placebo in minor adverse events and a single case of worsening depression in the pregabalin group.¹²⁴ The use of amine reuptake inhibitors in the pediatric and adolescent population has particular risks. In 2004, the US Food and Drug Administration directed manufacturers of all amine reuptake inhibitors (including selected SNRIs and TCAs) to include a warning stating that these drugs may increase the risk of suicidal ideation and behavior in children and adolescents.¹²⁵ These are clearly outlined in the remarks for recommendations 6a and 6b.

Rationale and key driver for recommendations. The panel concluded that the balance of benefits vs harms varies. This variability is reflected in the tailored approach that the panel has put forth for these recommendations. Furthermore, these recommendations emphasize the individualized treatment approach (ie, not one size fits all) required for the management of chronic pain. In summary, data supporting these recommendations rely heavily on indirect evidence; thus, there is very low certainty in the evidence about effects for patients with SCD. Ultimately, considering the available indirect data and the lack of direct data, the panel concluded that the decision to initiate and continue chronic nonopioid therapy for chronic SCD pain without an identifiable cause beyond SCD should be individualized (see recommendations 9a, 9b, and 9c) and based on a balance of benefits for that individual patient, harms, risk assessment, and shared decision making between the provider and patient with ongoing reassessment of the above issues. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepro.org/profile/a8898e09b30265e2956fe0fa22eb4942>.

Other EtD criteria and considerations. The panel acknowledges that there was no important uncertainty or variability about how much people value the main outcomes that were considered. Patients place significant importance on pain relief and improved functioning with the fewest adverse effects. The panel, including the patient representatives, concluded that patients and providers place high value on drugs that are opioid sparing and result in improved pain outcomes. The decision to use such drugs should include a discussion of the risks and the indirect evidence that addresses the benefits of chronic nonopioid therapy for use as a sole pharmacological agent or in combination with an opioid to reduce the total opioid dose. The absence of data specifically for individuals with SCD should also be discussed. The panel concluded that this should be done proactively with all patients when they are in their baseline state of health. However, overall there is a lack of published data that address knowledge basis and preferences regarding chronic nonopioid therapy specifically in individuals with SCD and clinicians treating SCD, and the panel identified this as a research gap. The panel concluded that resources required to prescribe SNRIs, TCAs, and gabapentinoids are likely not increased above and beyond the current treatment. The cost savings compared with COT are likely negligible but may be larger when the costs of the frequent monitoring associated with COT are included. There is a lack of data that address this issue in individuals with SCD; therefore, the panel was unable to determine cost effectiveness of chronic nonopioid therapy. The panel acknowledges that these chronic nonopioid medications may not be accessible to all patients, potentially because of a lack of insurance coverage for some patients, which could have a negative impact on health equity. The panel also acknowledges that the acceptability of chronic nonopioid therapy likely varies based on the individual patient's and the treating clinician's experience and knowledge, and there is an absence of data to inform this issue. Finally, the panel concluded that it is probably acceptable and feasible to implement chronic nonopioid therapy; however, barriers may exist, including patient and clinician knowledge of these nonopioid analgesics and insurance limitations, all of which may affect implementation of this recommendation.

Conclusions and research needs. The ASH guideline panel suggests considering chronic nonopioid therapy based on a balance

of risks of therapy and individualized benefits in terms of functional outcomes. Initiation of therapy requires assessment and prediction of these risks and benefits and durability of benefit over time. These factors differ for each pharmaceutical class of medications; therefore, the recommendations are divided into 3 pharmaceutical groups addressing these factors. The panel determined that engaging patients in a discussion about chronic nonopioid therapy proactively during their baseline state of health is warranted. Harm reduction strategies for patients age <25 years on amine reuptake inhibitors with depression or other psychiatric disorders should be strongly considered, including close observation for clinical worsening of depression, suicidality, or unusual changes in behavior. Additionally, families and caregivers should be advised to closely observe the patient and to communicate with the treating clinician. Collaboration with pain specialists and implementation of interdisciplinary care should also be considered, if available.

Because of the absence of data addressing the efficacy, effectiveness, and harms of chronic nonopioid therapy in individuals with chronic SCD pain without an identifiable cause beyond SCD, the panel discussed the following research priorities for children, adolescents, and adults living with SCD: (1) research focused on investigations into the use of all nonopioid drugs in patients with SCD; (2) comparative-effectiveness studies between COT and nonopioid pharmacological therapies in chronic SCD pain; and (3) research focused on investigations into the use of medical cannabis, cannabis derivatives, and synthetic cannabinoids for chronic pain in patients with SCD. In addition to efficacy, this research should particularly focus on risks and adverse events in patients with SCD.

Nonpharmacological therapies for chronic pain in SCD

Should nonpharmacological therapies be used in addition to pharmacological therapy for the treatment of chronic pain in children and adults with SCD?

Recommendation 8a

For *adults and children* with SCD who have chronic pain related to SCD, the ASH guideline panel *suggests* cognitive and behavioral pain management strategies in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- The cognitive or behavioral pain management strategy with the broadest evidence base is CBT. Other strategies considered by the panel with lower-certainty evidence include ACT, mindfulness-based treatments, coping skills training, and operant therapy.
- This recommendation is based mainly on indirect evidence. The treatments that have been tested in SCD are in children with acute pain without establishing the presence of chronic pain or the intervention's effects on chronic pain. The outcomes assessed in SCD have not typically included pain intensity. The greater body of indirect evidence was drawn from the literature in individuals with fibromyalgia and nonspecific low back pain.

- No standardized, manualized universally accepted version of CBT is available for SCD in either adults or children. This is a significant clinical and translational research need. Nonetheless, such strategies have shown broad applicability in pediatric and adult chronic noncancer pain.
- Interventions based on CBT, coping skills training, and guided imagery have some evidence base for SCD, although mainly in children and for episodic pain.
- In other conditions, these methods are believed to have low risks and are portable in that patients can use the skills learned on their own after treatment, possibly with intermittent booster sessions.
- Time, financial costs, availability, training of therapists (ie, in chronic pain and SCD), and patient burden can be barriers to these types of psychological treatments that are being recommended.
- Cognitive and behavioral pain management strategies should be used in conjunction with other modalities as part of a comprehensive and multimodal pain management plan.
- Behavioral and cognitive strategies are optimal in a setting where the patient is motivated and there is access to appropriately trained personnel.

Recommendation 8b

For *adults* with SCD who have chronic pain related to SCD, the ASH guideline panel *suggests* other provider-delivered integrative approaches (eg, massage therapy and acupuncture) as available, as tolerated, and conditional upon individual patient preference and response. These approaches should be delivered in the context of a comprehensive disease and pain management plan (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Time, financial costs, availability, training of therapists (ie, chronic pain and SCD), and patient burden can be barriers to these types of treatments.
- There is currently a lack of evidence in children; however, some pediatric patients may be using these treatments at home.

No recommendation

For *adults and children* with SCD who have chronic pain related to SCD, the ASH guideline panel chooses not to offer a recommendation for or against a number of physical activities, exercise, or combined meditation/movement programs (including aerobic exercise, yoga, and Pilates) to improve pain and disability.

Remarks:

- If physical activities, exercise, or combined meditation/movement programs (including aerobic exercise, yoga, and Pilates) are considered, a tailored approach is necessary that matches feasibility, tolerability, acceptability, and patient experience and preference regarding these interventions for a given patient.

- Discussion with patients during shared decision making needs to include important factors such as the time, financial costs, availability, and training of the people required to lead, teach, and perform these interventions.

Good practice statement

Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Recommendation 8a: cognitive and behavioral pain management strategies for treatment of chronic pain.

SPECIFIC BACKGROUND. A clinical hallmark of SCD is acute recurrent vasoocclusive episodes of pain. However, many children and adults with SCD also experience ongoing chronic pain. The first line of treatment of SCD pain is standard medical therapy, primarily NSAIDs and opioids. The panel agreed that pharmacotherapy alone has limited effectiveness in reducing the burden of chronic pain and associated psychosocial consequences in children and adults with SCD. Nonpharmacological strategies include psychological techniques (CBT, mindfulness, ACT, coping skills training), physical therapies (eg, exercise, physical activities, yoga), and integrative medicine approaches (eg, massage, acupuncture, complementary and alternative therapies), which are being used by patients with SCD. Therefore, the panel sought to systematically review the existing data and appraise the evidence to determine whether nonpharmacological therapies should be used to improve outcomes relative to solely pharmacological therapies (eg, opioids, NSAIDs, and others) or usual care for the management of chronic pain. Particular attention was paid to the impact on patient-centered outcomes, including improved pain intensity, pain coping strategies, reduction in chronic opioid consumption (daily dose of MME), health care encounters (ED visits and hospitalizations), HRQOL, functional outcomes, sleep, mood, and patient and clinician global impression of change.

SUMMARY OF THE EVIDENCE. The systematic review identified 10 studies that addressed this question from the direct literature in children and adults with SCD. Of these studies, there were 3 RCTs¹²⁶⁻¹²⁸ focused on CBT (single session with home-based practice for 8 weeks, family-based CBT, and community-based CBT) and 1 on coping skills training.¹²⁹ Of the 3 RCTs on CBT, 2 were conducted in pediatric populations (age ranges, 8-21 and 12-18 years),^{126,127} and the other was conducted in young adults (age range, 15-35 years).¹²⁸ The RCT on coping skills training was conducted in adults.¹²⁹ There were 2 observational studies examining guided imagery in children 6 to 11 years of age¹³⁰ and self-hypnosis in children and adults (age range, 5-60 years).¹³¹ Importantly, none of these studies specifically addressed chronic pain but focused more on recurrent acute painful episodes. Evidence for the following outcomes existed: (1) pain: overall decrease in pain intensity (high to moderate certainty)¹²⁶; (2) coping skills: improved coping skills (moderate to high certainty) and lower levels of negative thinking (high certainty)^{126,129}; pain sensitivity: lower pain sensitivity to noxious stimulus (high certainty)¹²⁹; (3) HRQOL: improvement in aspects of

QOL (moderate to high certainty)^{126,132}; and (4) self-efficacy: increased self-efficacy (low certainty).¹³⁰ There were no differences found in outcomes related to functional activity,¹²⁶ percentage of pain days, percentage of school days missed, and routine health care utilization.¹²⁷ There were no studies identified that addressed the following patient-centered outcomes: sleep, reduction in opioid use, mood, and patient and clinician global assessment of change. Because there were only 4 RCTs, the recommendation was downgraded to conditional based on certainty of the evidence ranging from low to intermediate. Because of the lack of direct evidence, 2 systematic reviews that focused on CBT from the indirect literature in chronic noncancer pain (primarily fibromyalgia and nonspecific low back pain) were reviewed.^{133,134} In the low back pain population, there were long-term improvements in pain, disability, and QOL.^{133,134} There were improvements in pain intensity and depressive mood and less health care use in those with fibromyalgia.¹³⁵ There was limited and low-quality evidence on other psychology-based strategies, such as mindfulness¹³⁶ and acceptance- and commitment-based therapies.

BENEFITS. The potential benefits of using cognitive behavioral and coping skills pain management strategies in the context of a comprehensive disease pain management plan are low to moderate and include improved pain control,¹³⁷ pain coping skills (ie, more adaptive coping and reduced negative thinking),^{126,129} and HRQOL.^{126,132} In other conditions, these psychological strategies are believed to have low risks, and once learned, these treatments are portable in that they can be done in any environment (hospital, home, work, or school) with intermittent booster skills training.

HARMS AND BURDEN. The panel discussed the fact that these psychological therapies have a low risk of harm. However, these are typically active strategies, which require significant time and effort on the part of the patient. Accessibility is likely to be limited by financial considerations because of incomplete insurance coverage and availability of appropriately trained and experienced therapists. Technological innovations, such as the use of mobile applications, may improve accessibility, but such interventions are in early stages of development.

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. Although evidence was minimal, balance of benefits vs harms likely favors the intervention. The panel identified few undesirable effects of the intervention except for the time commitment and cost of these therapies. As noted, there were only 4 small RCTs,¹²⁶⁻¹²⁹ mainly in children and for episodic pain, as well as indirect evidence from low back pain and fibromyalgia, which led to the downgrading of the recommendation to conditional based on very low certainty in the evidence about effects.

CONCLUSIONS AND RESEARCH NEEDS FOR THIS RECOMMENDATION. The guideline panel determined that there is overall low-certainty evidence for a net benefit of psychological therapies, including CBT and coping skills training, to treat chronic pain in SCD. This recommendation is justified based on the 4 RCTs primarily in pediatric SCD populations and indirect evidence from systematic reviews in chronic noncancer pain populations. The panel acknowledges that pain treatment using psychological therapies is typically multifaceted, including >1 approach (CBT, coping skills training, mindfulness, and operant training) and combined with other treatment modalities.

The panel identified the following additional areas of research that are needed: (1) delineate what cognitive, behavioral, or other nonpharmacologic techniques are most acceptable and effective for patients with SCD and chronic pain; (2) develop manualized or otherwise standardized interventions that are practical, meaning

accessible, developmentally appropriate, and with minimal burden; and (3) validate the resulting interventions with RCTs in children and adults with SCD suffering from chronic pain.

Recommendation 8b: provider-delivered integrative approaches (eg, massage therapy and acupuncture) for treatment of chronic pain.

SPECIFIC BACKGROUND. As outlined above, a variety of provider-delivered integrative approaches (eg, massage therapy and acupuncture) are available. These are passive modalities and are dependent on patient preference and response to these treatments.

SUMMARY OF THE EVIDENCE. The systematic review identified several studies that addressed this broader question from the direct literature in children and adults with SCD. Of these studies, 4 focused on provider-delivered integrative approaches. There was 1 small-scale RCT of massage in adults (mean age, 32.8 years),¹³⁸ 1 observational study of acupuncture in adults (age range, 19-67 years),⁶⁶ 2 single-arm pilot studies of biofeedback in children (age range, 7-17 years),¹³² and 1 in children and young adults (age range, 10-20 years).¹³⁹ Evidence for the following outcomes existed, all with very low certainty in the evidence about effects: (1) pain intensity,¹³⁸ (2) functioning,¹³² (3) HRQOL,¹³² (4) anxiety,¹³⁹ (5) intensity and frequency of pain episodes,¹³⁹ (6) number of days analgesics were used,¹³⁹ and (7) global impression of treatment effectiveness,¹³⁹ rated as fair to very effective. There were no differences found in outcomes related to functional activity,¹³² proportion of pain days,¹³¹ proportion of school days missed,¹³¹ and hospital visits for SCD.¹³⁹ There were no studies identified that addressed the following patient-centered outcomes: sleep, mood, and clinician global assessment of change. Because there was only 1 RCT and the other studies were observational, the recommendation was downgraded to conditional based on the low certainty in evidence. Because of the lack of direct evidence, indirect evidence was examined. One systematic review from the indirect literature in fibromyalgia found that massage therapy for ≥ 5 weeks had immediate beneficial effects on pain, anxiety, and depression.¹⁴⁰ In terms of indirect evidence for acupuncture, 3 systematic reviews on chronic low back pain¹⁴¹⁻¹⁴⁴ found evidence of favorable effects on pain intensity and functional limitations/disability in short-term use. However, all reviews cited insufficient methodological rigor of the trials included, and there were no studies of pediatric patients.

BENEFITS. The potential benefits of using provider-delivered integrative pain management approaches in the context of a comprehensive disease pain management plan are low and include improved pain control, functioning,¹³² and HRQOL¹³² and reduced anxiety,¹³⁹ frequency of pain episodes,^{132,139} and medication use.¹³⁹ In other conditions, these provider-delivered integrative approaches are believed to have low risks and are helpful in combination with conventional treatments (ie, pharmacological and psychological).

HARMS AND BURDEN. The panel discussed the fact that these provider-delivered integrative therapies have low risk of harm. However, there is potentially significant time commitment and thus need for the patient to be motivated, and there are financial costs to these therapies. These therapies require training, and therefore, it may be more difficult to find personnel who are adequately trained. Finally, in 1 study where family members delivered the massage therapy, the participants actually felt worse, so there might be some risks for others delivering this type of intervention.

RATIONALE AND KEY DRIVER FOR RECOMMENDATION. The balance of benefits vs harms favors the intervention. The panel identified few undesirable effects of the intervention except for the time commitment and cost of these therapies. Overall, the balance of effects favored the intervention. This recommendation was downgraded to conditional, because there was only 1 small RCT in SCD, with the other studies being observational or single-arm pilot studies, and the pain being treated was episodic, as well as indirect evidence from the chronic low back pain population.

CONCLUSIONS AND RESEARCH NEEDS FOR THIS RECOMMENDATION. The guideline panel determined that there is overall very low certainty in the evidence for a net benefit of provider-delivered integrative therapies, including massage and acupuncture, regarding patient-important outcomes associated with the treatment of chronic pain in patients with SCD. This recommendation is justified based on the 1 RCT and 3 observational/single-arm pilot studies in primarily adults with SCD and indirect evidence from systematic reviews in adult chronic low back pain populations. The panel acknowledges that pain treatment using provider-delivered therapies is typically combined with other pharmacological, psychological, and physical strategies.

The panel identified the following additional areas of research that are needed: (1) larger-scale, adequately controlled clinical trials of massage therapy and acupuncture for chronic pain in SCD should be conducted and (2) as for cognitive, behavioral, and other psychotherapeutic interventions noted above, these interventions should be acceptable and accessible, with minimal patient burden, and defined well enough to be reproducible across multiple settings.

No recommendation: physical activities, exercise, or combined meditation/movement programs (including aerobic exercise, yoga, and Pilates) for treatment of chronic pain.

SPECIFIC BACKGROUND. There are a number of physical activities, exercise, or combined meditation/movement programs that may be used to help with chronic pain to improve pain and disability. Physical therapists typically provide these interventions and are a key part of multidisciplinary pain teams.

SUMMARY OF THE EVIDENCE. The systematic review identified no direct studies that evaluated the impact of physical activities, exercise, or combined meditation/movement programs on clinical outcomes of interest in patients with SCD. Because of the lack of direct evidence, indirect evidence for other conditions (chronic low back pain and fibromyalgia) was examined. There was 1 systematic review on Pilates¹⁴⁵ that found a reduction in pain intensity in chronic low back pain and 6 systematic reviews on physical activity that found small improvements in pain intensity and disability (2 in fibromyalgia^{146,147} and 4 in chronic low back pain^{133,148-150}). However, there was large variability in the components of the physical activities studied. Finally, there were 2 reviews on core stability exercise^{151,152} for chronic low back pain that found conflicting results of the impact on pain and disability. Therefore, no recommendation could be made for or against these therapies because of the speculative nature of the indirect evidence in patients with chronic low back pain and fibromyalgia.

BENEFITS. There was no direct evidence on the benefits of these movement-based approaches. There was some speculative indirect evidence of benefits in improved pain control and functional disability^{149,150} in other chronic pain conditions.

HARMS AND BURDEN. It is not known whether these movement-based therapies are tolerable in pediatric or adult patients with SCD. Their use in this population may be complicated by exertion sensitivity, the importance of hydration, and anemia.

RATIONALE. The guideline panel determined that there is no direct evidence and overall very low certainty in the indirect evidence in populations with fibromyalgia and low back pain for the use of physical activities, exercise, or combined meditation/movement programs (including aerobic exercise, yoga, and Pilates) for the management of chronic pain in SCD, and therefore, a recommendation for or against the use of these movement-based therapies could not be made. The panel identified few undesirable effects of movement-based therapies; however, exercise tolerance, exertion sensitivity, hydration, and anemia may limit acceptability and feasibility for individuals living with SCD.

CONCLUSIONS AND RESEARCH NEEDS. The panel identified the following additional area of research that is needed: larger-scale, adequately controlled clinical trials of physical activities and exercise and movement-based programs for chronic pain in SCD to determine the efficacy, safety, and effectiveness of these interventions.

Other EtD criteria and considerations. The evidence base for the interventions surveyed was relatively small and often indirect, but the panel concluded that the treatment of chronic pain in patients with SCD was a priority and that there is probably no important uncertainty in its value to patients as well. Although the panel expected that desirable effects overall might be small, the panel also concluded that undesirable effects were smaller, and the benefits outweighed them. The panel discussed the fact that CBTs can have risks if improperly delivered. One of these risks is a paradoxical increase in pain perception. Regarding the interventions, the panel, especially the patient representatives, concluded that patients prefer options for pain management that include integrative therapies. Patients likely desire options that allow them to have control over their symptoms and that facilitate opioid avoidance. It is desirable to have coping strategies, and generally, the panel believed that patients would be willing to dedicate time to learn skills such as CBT. Furthermore, the portability of the intervention and improving capacity for self-management were desirable effects. Overall, the panel concluded that the patient resources needed, including financial costs, time, and effort, were likely to be moderate, although there was little evidence to support this conclusion. For health systems, the resources required are primarily centered around the need to have appropriately trained personnel and necessary devices to administer these interventions. The panel noted that patients could be trained to self-administer some of the interventions, which could reduce resources required. There was minimal evidence to establish cost effectiveness. The panel concluded that most patients, families, and providers would agree that the implementation and use of nonpharmacological interventions are probably acceptable. The panel noted that some interventions may not be feasible for all age groups, especially very young children. The panel also raised important concerns that some third-party payers, including state Medicaid programs, may not cover CBT, which could limit the feasibility of the intervention. CBT programs can be tailored to the needs of the population and could be delivered via Web-based programs. Data support the acceptability and feasibility of Web-based CBT¹²⁶ in adolescents with SCD. The complete EtD framework for this question, including evidence tables,

is provided as an online supplement: <https://guidelines.gradepr.org/profile/46dec276a2216e50a94e299f2e6b7598>.

COT for chronic pain in SCD

Should COT vs no COT or periodic opioid therapy be used in patients with SCD who have chronic pain?

Introduction. The ASH guideline panel suggests an individualized approach to initiating or discontinuing COT that is based on the balance between risks/harms and benefits and should consider functional outcomes and the durability of benefit over time. The panel's recommendations are divided based on 3 distinct patient populations who have the clear presence of chronic (rather than episodic) pain. The panel based these recommendations on the following definitions for COT: (1) patients receiving a ≥ 70 -day supply of opioids in a 90-day period or (2) an index opioid prescription in the past 4 months followed by at least 2 more opioid prescriptions and having at least a 60-day supply of opioids within the 4-month period. The index prescription had to follow a period of at least 3 months without an opioid prescription being filled.

Good practice statement

It is good practice to deliver patient-centered education regarding the potential to develop chronic pain and the nonopioid pain treatment options that are outlined in recommendations 6, 7, and 8.

Recommendation 9a

For *adults and children* with SCD and emerging and/or recently developed chronic pain, the ASH guideline panel *suggests against* the initiation of COT unless pain is refractory to multiple other treatment modalities (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.
- In those whose pain has been refractory to multiple other interventions, COT should be considered after risk stratification using a validated tool, based on how well patients' SCD is managed, comprehensive assessment of behavioral risks (eg, risk factors for opioid misuse), implications of tolerance on the management of acute pain episodes, and other known adverse effects of opioids. Adverse events noted in other non-SCD patient populations are dose dependent and include increased risk of poor surgical outcomes, increased risk of motor vehicle collisions, myocardial infarction, bone fracture, and mortality. Patients on doses of > 120 mg MME are at risk for hormonal alterations, which can lead to sexual dysfunction. Doses > 100 mg MME are associated with a ninefold increase in risk of overdose compared with doses < 20 mg MME in general non-SCD pain populations.
- Failure criteria for a trial of COT should be discussed in the shared decision-making process, and alternative treatments in the case of failure and a plan for opioid cessation should be developed before initiation. Documentation of this discussion and the goals of care should be included in the medical record.
- The lowest effective opioid dose should be prescribed.

- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Providers should be aware that patients may inadvertently end up on COT if episodic pain is frequent enough that patients are receiving frequent opioid treatment of recurrent pain. Therefore, providers should make efforts to reduce or eliminate scheduled opioid doses between acute episodic pain events, which may reduce the likelihood of unintentional COT.

Recommendation 9b

For *adults and children* with chronic pain from SCD who are receiving COT, are functioning well, and have perceived benefit, the ASH guideline panel *suggests* shared decision making for continuation of COT (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.
- The benefit of COT in SCD is largely unknown, and the harms are established via indirect evidence (recommendation 9a, remark 2); therefore, shared decision making is essential and may lead to continuation once risks of COT and tapering are explained.
- Function should be assessed from the shared patient/clinician perspective. The use of standardized patient-reported outcome tools that assess patient functioning is encouraged.
- COT is discussed as a class of drugs. Individual opioid drugs have different specific toxicity profiles and interactions with end-organ injury. Therefore, a review of the individual profile of each drug under consideration for use should be performed for a given patient.
- The lowest effective opioid dose should be prescribed.
- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Patients on COT require careful monitoring with regard to functional status and risk assessment for the development of aberrant opioid use and medical, social, behavioral, or psychological complications as a precursor to opioid dose reduction or weaning.
- The risk of adverse events related to COT rises as the total dose increases. Therefore, patients on high doses of opioids need close monitoring for complications and adverse effects.

Recommendation 9c

For *adults and children* with chronic pain from SCD who are receiving COT, are functioning poorly, or are at high risk for aberrant opioid use or toxicity, the ASH guideline panel *suggests against* continuation of COT (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- Optimization of SCD management is a priority.

- Collaboration with a pain specialist should be strongly considered for additional or alternative pain management strategies.
- Weaning and/or withdrawal from COT is potentially a higher-risk entity in patients with SCD (ie, risk of triggering vasoocclusive events or other medical complications) and should be done carefully.
- The other recommendations provided in this summary should be used for potential alternatives that could be part of a comprehensive pain management plan.
- Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.
- Acute pain events may still be treated with opioid analgesia if this serves the overall pain treatment plan, but this should be done in conjunction with the primary outpatient management team. Furthermore, nonopioid medications and integrative therapies should also be offered as outlined in prior recommendations.

Good practice statement

It is good practice to implement harm reduction strategies for patients on COT, including strongly considering coprescribing naloxone, avoiding coprescribing opioids and benzodiazepines, and prescribing the lowest effective opioid dose.

Good practice statement

It is good practice to consider collaboration with pain medicine specialists for the management of individuals living with SCD who have chronic pain.

Good practice statement

In cases in which the clinician has valid and substantial evidence of aberrant opioid use, it is good practice to consider consulting an addiction medicine physician.

Good practice statement

It is good practice to provide patient-centered education regarding the risks of chronic opioid therapy.

Good practice statement

Given the prevalence of psychological comorbidities that are present in the context of pain, it is good practice to routinely screen for depression and anxiety and to perform targeted screening for other psychological comorbidities.

Specific background. Individuals living with SCD suffer from chronic pain. The prevalence of chronic pain increases with age and can be associated with an identifiable cause (eg, avascular necrosis or leg ulcers) or a nonidentifiable cause. COT is often used to manage the chronic pain suffered by individuals with SCD. There is currently a paucity of evidence-based guidelines that address the use of COT for chronic SCD pain. Therefore, a systematic review of existing data was conducted with an appraisal of the evidence for the impact of COT on patient-important outcomes, including the efficacy, effectiveness, and harms. Data reviewed included both pediatric and adult populations to inform this question and recommendation. The panel based these recommendations on the following definitions for COT: (1) patients receiving a ≥70-day

supply of opioids in a 90-day period¹⁵³ or (2) an index opioid prescription in the past 4 months followed by at least 2 more opioid prescriptions and having at least a 60-day supply of opioids within the 4-month period. The index prescription had to follow a period of at least 3 months without an opioid prescription being filled.¹⁵⁴

Summary of the evidence. The systematic review did not identify any direct evidence in patients with SCD that informed this question. Therefore, the panel agreed to search the indirect evidence for chronic noncancer pain populations other than SCD. The indirect evidence review was restricted to published systematic reviews and meta-analyses that addressed the use of COT for chronic noncancer pain in pediatric and adult populations. This review identified 5 publications that were included in the evidence profile, 3 of which were the most currently available Cochrane Database systematic reviews. Of these 5 reviews, only 1 addressed the use of opioids for chronic noncancer pain in children and adolescents, and the remainder were focused on adult populations. One Cochrane review¹⁵⁵ specifically assessed high-dose opioids (≥ 200 mg of morphine equivalent daily) for chronic noncancer pain. Evidence from these 5 systematic reviews/meta-analyses addressed the following outcomes: pain relief, functional outcomes, and long-term harm. Regarding pain relief and functional outcomes, a key point from the data synthesis was that to date, there is a paucity of high-quality research from which to draw reliable conclusions about the efficacy or effectiveness of long-term COT for chronic noncancer pain in both pediatric and adult populations. Importantly, no studies that were included in the systematic reviews and meta-analyses followed patients beyond 6 months. One systematic review/meta-analysis¹⁵⁶ included 42 RCTs ($n = 16\,617$) and concluded that opioids were associated with reduced pain compared with placebo on a 10-cm VAS used for pain assessment. However, the impact of opioids on function, as assessed by the 36-item Short Form Health Survey, compared with placebo was mixed. Opioids compared with placebo were associated with small improvements in physical functioning and social functioning, but the criterion for the minimally important difference was not met. Opioids, compared with placebo, had no impact on emotional functioning and mixed results for the role functioning subscale for role limitations resulting from physical problems. The same review¹⁵⁶ also sought to compare the effectiveness of opioids and nonopioid pharmacological pain therapies (eg, NSAIDs, TCAs, and anticonvulsants), with a focus on the outcomes of pain relief and functioning. The evidence for the effectiveness of opioids for pain relief as measured on a quantitative scale (VAS) compared with these other pharmacological treatments was mixed. In summary, 9 RCTs ($n = 1431$) showed no difference in pain relief between opioids and NSAIDs, 3 RCTs ($n = 246$) showed no difference in pain relief between opioids and nortriptyline (TCA), and 3 RCTs ($n = 303$) suggested that opioids were associated with greater pain relief than anticonvulsants. Busse et al¹⁵⁶ also compared the impact of COT and the same nonopioid pharmacological therapies on functional outcomes assessed with the 36-item Short Form Health Survey. In summary, data from 7 RCTs ($n = 1311$) showed no difference in physical functioning between opioids and NSAIDs, and small studies of low-quality evidence suggested no difference in physical functioning between opioids and TCAs (2 studies; $n = 158$) and between opioids and anticonvulsants (3 RCTs; $n = 303$). Chou et al¹⁵⁷ published a systematic review in 2015 and found no published data that assessed the effectiveness of chronic

long-term opioid therapy (defined as >1 year) compared with no opioid therapy or nonopioid therapy. A Cochrane systematic review evaluated 26 studies ($n = 4893$) that included 25 case series and 1 RCT.¹⁵⁸ This review concluded that weak evidence existed that clinically significant pain relief occurs in patients who can continue long-term COT. The authors were unable to determine impact on functioning because of inconclusive evidence. A single Cochrane systematic review addressed the use of high-dose opioids (≥ 200 mg of MME) for chronic noncancer pain.¹⁵⁵ This review did not identify any included studies and concluded there was a critical lack of evidence regarding the efficacy/effectiveness of high-dose opioids for the treatment of chronic noncancer pain. Finally, a single Cochrane systematic review was identified that addressed the use of opioids for chronic noncancer pain in children and adolescents.¹⁵⁹ This review did not identify any RCTs that addressed this topic. Therefore, the authors concluded that there was an absence of evidence to either support or refute the use of opioids for the treatment of pediatric patients suffering from chronic noncancer pain.

The panel also assessed the risk of harm associated with the use of COT. In summary, the systematic review did not identify any direct evidence in patients with SCD that informed this question. Indirect evidence in chronic noncancer pain populations showed that there is increased risk of significant harm related to COT. A systematic review included 19 RCTs and observational studies that support this assessment.¹⁵⁷ The specific harms are outlined in detail below in "Harms and burden." Ultimately, because only indirect data were available to address this question, all recommendations were downgraded to conditional based on very low certainty in the evidence.

Benefits. There is a significant absence of data that address the desirable effects of COT in individuals living with SCD. Therefore, all data reviewed were from published systematic reviews and meta-analyses conducted in other chronic noncancer pain populations. In general, there is a paucity of high-quality data that assess the benefits of long-term COT for chronic noncancer pain. Indirect data that discuss the potential benefits identified and synthesized by the panel are outlined above. There may be some benefit of COT over placebo for pain relief; however, data assessing the benefit of COT compared with other nonopioid analgesics show mixed results. Notably, there is an absence of data assessing the benefits of COT in children and adolescent populations. Therefore, the panel concluded that the true benefit of COT for individuals living with SCD and suffering from chronic pain is largely unknown.

Harms and burden. The panel discussed the known risks of COT that have been published in the indirect literature in chronic noncancer pain populations. These are clearly outlined in the remarks for recommendation 9b. These include but are not limited to increased risk of poor surgical outcomes,¹⁶⁰ motor vehicle collisions,¹⁶¹ myocardial infarction,¹⁶² bone fracture,¹⁶³ sexual dysfunction,¹⁶⁴ and mortality.^{165,166} Adverse events are dose dependent. Patients on doses of >120 mg of morphine equivalent dosing are at risk for hormonal alterations, which can lead to sexual dysfunction.¹⁶⁴ In non-SCD pain populations, doses >100 mg of morphine equivalent dosing are associated with a ninefold increase in risk of overdose, compared with doses <20 mg of morphine equivalent dosing.^{165,167} Therefore, patients on high doses of opioids need close monitoring for complications and adverse effects.^{156,157} A single study on opioid-related deaths in individuals with SCD in the United States¹⁶⁸ showed 95 deaths attributable

to opioids were reported from 1999 to 2013. Opioid-related deaths in people without SCD reported in this study during the same timeframe was 174 959. Patients on COT should avoid the use of benzodiazepines, sedating medications, and alcohol.¹⁶⁹ Weaning and/or withdrawal from COT is potentially a higher-risk entity in patients with SCD (ie, risk of triggering vasoocclusive events or other medical complications) and should be done carefully.¹⁷⁰⁻¹⁷⁴ Notably, the harms related to COT in children and adolescents with SCD are largely unknown, because the Cochrane systematic review that addressed opioids for chronic noncancer pain in children and adolescents did not identify any studies to address this issue in the pediatric age group.

Rationale and key driver for recommendations. The panel concluded that the balance of benefits vs harms varies. This variability is reflected in the tailored approach that the panel has put forth for these recommendations. Furthermore, these recommendations emphasize the individualized treatment approach (ie, not one size fits all) is required for the management of chronic pain. The panel acknowledges that the evidence is insufficient to determine the efficacy and/or effectiveness of long-term opioid therapy for improving chronic pain and function in individuals living with SCD. Indirect evidence in chronic noncancer pain populations is also insufficient to determine long-term efficacy and/or effectiveness and supports risk for harms. It is unknown if these harms are the same in individuals with SCD. Ultimately, considering the available indirect data and the lack of direct data, the panel concluded that the decision to initiate, continue, or taper COT should be individualized (see recommendations 9a, 9b, and 9c) and based on a balance of benefits for that individual patient, harms, risk assessment, and shared decision making between the provider and patient with ongoing reassessment of the above issues. Because only indirect data were available to address this question, all recommendations were downgraded to conditional based on very low certainty in the evidence. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.grade-pro.org/profile/84c3f6dcfab4eb51c0f25e93cdb8c0b0>.

Other EtD criteria and considerations. The panel acknowledges that there was no important uncertainty or variability about how much people value the main outcomes that were considered. Patients place significant importance on pain relief and improved functioning with the fewest adverse effects. The panel, including the patient representatives, concluded that there is an important need to engage patients in a discussion about the use of COT for the treatment of chronic SCD pain before its initiation. This should include a discussion of the risks of COT and of the insufficient evidence that addresses the benefits of COT. The panel concluded that this should be done proactively with all patients when they are in their baseline state of health. However, overall there is a lack of published data that address values and preferences regarding COT specifically in individuals with SCD, and the panel identified this as a research gap. The panel acknowledges that individuals living with SCD who are receiving COT require frequent monitoring, which has associated financial costs. However, it is unknown whether these costs are different from costs associated with pain management strategies that do not involve opioid therapy. There is a lack of data addressing this issue in individuals with SCD; therefore, the panel was unable to determine cost effectiveness of COT. The panel acknowledges that alternatives to COT may not be accessible to all

patients, especially because of limited insurance reimbursement for many integrative therapies, which could have a negative impact on health equity. The panel also acknowledges that the acceptability of COT likely varies based on the individual patient and family, and there is an absence of data to inform this issue. The panel concluded that it is probably feasible to implement COT in appropriate patients as per the recommendations the panel has put forth; however, barriers may exist including access, prescribing restrictions, and insurance limitations, all of which may affect implementation of this recommendation. The panel concluded that function should be assessed from the shared patient/clinician perspective. The use of standardized patient-reported outcome tools that assess patient functioning is encouraged.^{175,176} The panel also discussed validated tools¹⁷⁷ that can be used for risk stratification and risk assessment for the development of aberrant opioid use.¹⁷⁸⁻¹⁸¹

Conclusions and research needs. The ASH guideline panel suggests considering COT based on a balance of risks of therapy and individualized benefits in terms of functional outcomes and on the clear presence of chronic (rather than episodic) pain (see the definitions of acute and chronic pain above). Initiation of therapy requires assessment and prediction of these risks and benefits, whereas continuation or discontinuation involves ongoing evaluation of adverse events, future risks, and durability of the benefits over time. Therefore, the recommendations are divided into heuristic definitions of patient populations addressing these factors. These populations are defined, and recommendations for each population are provided. The panel concluded that engaging patients in a discussion about COT proactively during their baseline state of health is warranted. Harm reduction strategies for patients on COT should be strongly considered, including coprescribing naloxone, prescribing the lowest effective dose of opioids, and avoiding coprescribing benzodiazepines. Collaboration with pain specialists and implementation of multidisciplinary and interdisciplinary care should also be considered, if available. Because of the absence of data addressing the efficacy, effectiveness, and harms of COT in individuals with SCD, the panel discussed the following research priorities for children, adolescents, and adults living with SCD: (1) investigations into the efficacy and effectiveness of COT for chronic pain; (2) investigations into the harms of COT; (3) investigations into patients' values and preferences regarding COT; (4) comparative-effectiveness studies between full agonist opioids and partial agonist opioid therapy, such as buprenorphine therapy; and (5) comparative-effectiveness studies between COT and nonopioid pharmacological therapies.

Chronic transfusion therapy for the treatment of recurrent acute pain and/or chronic pain

Should chronic monthly transfusion therapy to suppress hemoglobin S levels to <30% vs no transfusions or on-demand transfusions be used for children and adults with SCD who have recurrent acute pain and/or chronic pain?

Recommendation 10

For adults and children with SCD and recurrent acute pain, the ASH guideline panel suggests against chronic monthly transfusion therapy as a first-line strategy to prevent or reduce recurrent acute pain episodes (conditional recommendation based on low certainty in the evidence about effects ⊕⊕○○).

Remarks:

- In unique circumstances when all other measures to control recurrent pain episodes have failed (eg, hydroxyurea, other disease modifying therapies) and when shared decision making can be fully applied, a trial of monthly transfusions may be reasonable.
- The decision should be influenced primarily by patient preference where patients appreciate the uncertainty in benefit over the burden and risks of monthly transfusion. Integration of education and informed shared decision making around initiation and/or cessation of chronic transfusion therapy are important.
- IV access and adherence to chelation and erythrocytopenia are also considerations that could favor monthly transfusions in the exceptional circumstances noted above.
- The cessation of chronic transfusions can be associated with other SCD complications. Therefore, it is important to exercise caution if cessation of chronic transfusion is considered, including initiation of other disease-modifying therapies and increased surveillance.

No recommendation

For *adults and children* with chronic pain from SCD, the ASH guideline panel chooses not to offer a recommendation for or against chronic monthly transfusion therapy as an option for pain management.

Specific background. Some people with SCD have frequent episodes of acute SCD pain treated at home or in SCD-specific acute facilities, EDs, and hospitals.² These acute pain episodes negatively affect QOL and function and cause affected individuals to be absent from school, work, and other important activities. People with chronic SCD pain (as defined above) also have impairment in QOL and functional status.¹⁸ Three medications currently approved for the treatment of children and adults with SCD (hydroxyurea, L-glutamine, crizanlizumab) reduce the rate of acute pain episodes that are treated in acute care settings (EDs, infusion centers/day hospitals, and hospitals).¹⁸²⁻¹⁸⁴ However, some children and adults with SCD cannot tolerate these treatments or continue to have recurrent and frequent episodes of acute pain despite hydroxyurea and/or L-glutamine. Neither therapy is approved for the treatment of chronic pain in people with SCD, but hydroxyurea was recommended by the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report for the treatment of adults with sickle cell anemia and sickle cell–associated pain that interferes with daily activities (strong recommendation, moderate-quality evidence). However, this report did not address the use of red blood cell transfusion for recurrent acute pain or chronic pain in children or adults with SCD.¹⁸⁵ Therefore, the panel sought to systematically review the existing data and appraise the evidence to determine whether monthly transfusion should be used to prevent or reduce recurrent acute pain or chronic pain in this population. Particular attention was paid to the impact of transfusion on health care encounters for pain, HRQOL, functional outcomes, sleep, mood (anxiety, depression), reduction in COT, pain intensity, and patient and clinician global impression of change.

Recommendation 10: chronic transfusion therapy for treatment of recurrent acute pain.

SUMMARY OF THE EVIDENCE. The systematic review identified 7 studies that compared the rate of acute painful events in transfused vs untransfused children and adults with sickle cell anemia. Of these, there were 4 RCTs enrolling a total of 439 children and 72 pregnant women and 3 studies comparing rates before and after starting transfusions (31 children and 15 adults).¹⁸⁶⁻¹⁹² Evidence was of very low certainty, because all of the RCTs enrolled participants with other indications for transfusion (silent stroke, stroke, abnormal transcranial Doppler ultrasound, or pregnancy). Therefore, few participants had frequent recurrent pain or chronic pain at the time of study entry. The only studies to include a substantial proportion of people with recurrent acute pain at entry were small (13 to 17 participants) and compared rates of painful events before and after the start of transfusions.^{187,191,192} None of these studies reported on the impact of chronic transfusions on HRQOL outcomes that are associated with pain and function, thereby making the data using health care utilization as an outcome a likely underestimate of the pain burden.

BENEFITS. The potential benefits of chronic transfusion for recurrent pain are largely unknown. Most data are for children, and transfusions were initiated for reasons other than pain (stroke, silent stroke, abnormal transcranial Doppler ultrasound, or pregnancy). In the transfused arms, the rate of acute pain episodes decreased by 17 to 61 per 100 person-years in children and from 50% to 16% (proportion) during pregnancy.¹⁸⁸⁻¹⁹⁰ There were 2 studies with very low certainty in the evidence in small cohorts of patients that showed that transfusions may decrease health care utilization for pain.^{187,191,192} There was a lack of comparative-effectiveness data between hydroxyurea and other disease-modifying therapies and chronic transfusions.

HARMS AND BURDEN. The panel discussed the fact that monthly red blood cell transfusion has a moderate risk of harm and a very high burden. Specifically, the panel discussed iron overload, monthly visits and chelation, IV access issues that may require central venous access, alloimmunization to red blood cell antigens, and transfusion reactions. Also, the panel agreed that significant time, personnel commitment, and moderately high costs are required to deliver these therapies.

RATIONALE AND KEY DRIVERS FOR RECOMMENDATION. The panel acknowledges that the evidence for efficacy of monthly transfusion for the treatment of recurrent acute SCD pain is limited and of low methodological quality. In addition, potential harms, burdens, and costs were substantial. Overall, the panel determined that the balance of effects favors the comparison, leading to a conditional recommendation against the intervention. The limited and low-quality evidence of efficacy and moderate evidence of harms led to the conditional recommendation. The complete EtD framework for this question, including evidence tables, is provided as an online supplement: <https://guidelines.gradepro.org/profile/f4c6c900bf9e6d0e10264fdd1b866f8f>.

OTHER ETD CRITERIA AND CONSIDERATIONS. The guideline panel acknowledges that the systematic review identified very limited data on the specific population of interest, those with recurrent acute SCD pain. The only RCTs, despite being in people with sickle cell anemia, represented indirect evidence because of a different study population (the indication for transfusion was not pain).

The panel also discussed the fact that it may not be feasible to deliver transfusion safely in all settings secondary to an increased risk of complication (alloimmunization or iron overload) in people

with SCD. The panel felt that there is moderate certainty in the evidence of the resources required to implement these interventions. The panel acknowledges that there was possibly important uncertainty or variability about how much patients value the main outcomes that were considered. The data on cost effectiveness were too limited to develop conclusions. The panel concluded that these interventions would probably not be acceptable to patients in the absence of data about true benefit.

CONCLUSIONS AND RESEARCH NEEDS. The guideline panel determined that there is overall very low certainty in the evidence for a net harm of monthly transfusion of red blood cells to prevent or reduce acute pain episodes in patients with SCD. Despite the absence of direct evidence for acute recurrent pain, this conclusion is reasonable given the high prevalence of potential harms from monthly blood transfusions and the absence of high-quality data showing effect. The panel identified the following additional areas of research that are needed: (1) comparative-effectiveness research to compare chronic transfusions with hydroxyurea and other disease-modifying therapies for recurrent acute and chronic pain; (2) research on the impact of chronic transfusion therapy on the patient-centered outcomes outlined above, including HRQOL; and (3) investigations that identify the appropriate trough hemoglobin S percentage for the treatment of recurrent acute or chronic SCD pain.

No recommendation: chronic transfusion therapy for treatment of chronic pain.

SUMMARY OF THE EVIDENCE. The panel did not identify any direct evidence that addressed this question. Furthermore, the panel concluded that indirect evidence was not applicable to this question.

BENEFITS. The panel did not identify any direct evidence that addressed this question. Furthermore, the panel concluded that indirect evidence was not applicable to this question.

HARMS AND BURDEN. The harms and burden of chronic transfusion therapy for chronic pain are similar to those previously outlined when the therapy is used for other indications (see above for recommendation 10).

RATIONALE. Because of the absence of evidence for chronic pain, a recommendation for or against the use of chronic transfusion therapy could not be made. The panel agreed that indirect evidence was not relevant to this question.

CONCLUSIONS AND RESEARCH NEEDS. Given the high prevalence and impact of chronic pain, investigations that address how chronic transfusion therapy affects chronic pain should be prioritized. The panel identified the following additional types of research that are needed: (1) impact of chronic transfusion therapy on chronic pain-related morbidity with assessment of patient-centered outcomes, including HRQOL; (2) the impact of chronic transfusion therapy on COT; and (3) the impact of chronic transfusion therapy on measures of pain sensitization.

General comments regarding treatment of chronic pain

With respect to recommendations for the treatment of chronic pain, unfortunately, the evidence base in SCD directly addressing this serious issue is grossly deficient, and rectifying this should be a high priority for research in the field. The panel agreed that in practice, the treatment of chronic pain has extended from and mirrored treatment of acute pain in SCD, which is not likely to produce

optimal results. These guidelines focused on the evidence base supporting individual interventions for chronic pain in SCD. However, the panel agreed that another important clinical matter is the lack of an integrated, evidence-supported multidisciplinary and interdisciplinary treatment model for chronic pain in SCD. This model would leverage evidence and expertise from the fields of hematology, pain medicine, psychiatry, psychology, nursing, physical therapy, occupational therapy, and other disciplines to help patients achieve maximal function and QOL while minimizing risks and interference from treatment. As a matter of policy, the panel believes that the development of infrastructure and funding models to support such interventions and investigations into the efficacy and effectiveness of such interventions is an important and necessary goal. Furthermore, research into system barriers and solutions to these barriers is needed to provide the evidence base that can facilitate successful implementation of such a care model.

What are others saying, and what is new in these ASH guidelines?

Acute and chronic pain management for patients with SCD is addressed within existing evidence-based guidelines. Selected guidelines include the following: (1) NHLBI, “Expert Panel Report of the Evidence-Based Management of Sickle Cell Disease” (2014)¹⁹³; (2) American Pain Society, “Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease” (1999)¹⁹⁴, and (3) National Health Service National Institute for Health and Care Excellence, “Sickle Cell Acute Painful Episode: Management of an Acute Painful Sickle Cell Episode in Hospital” (2012).¹⁹⁵ The current pain management recommendations put forth by the ASH guideline panel need to be considered in the context of the recommendations that already exist.

The most recent guidelines that address acute SCD pain include the NHLBI guidelines (2014)¹⁹³ and the National Institute for Health and Care Excellence guidelines (2012).¹⁹⁵ The ASH guidelines provide new recommendations for acute pain that were not included in these prior guidelines. Specifically, the ASH guidelines include additional and more extensive recommendations for nonopioid-based pharmacological therapy (recommendation 2) and nonpharmacological therapy (recommendation 3). In addition, the ASH guidelines address alternative sites of acute pain care delivery (recommendation 4). The ASH guidelines also put forth a stronger recommendation based on available evidence for personalized opioid dosing for acute pain (recommendation 1). This recommendation was based on evidence from an RCT published after the NHLBI guidelines¹⁹³ were released that assessed the efficacy of a personalized dosing protocol. Our guidelines align with these guidelines for rapidity of analgesic delivery and frequent reassessments between pain medication doses (recommendation 1).

Because chronic pain is now recognized as a distinct entity in patients with SCD, the ASH guideline panel had the opportunity to do a more in-depth evaluation of the available evidence for chronic pain management. The ASH guidelines use the “AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain”¹⁸ to frame questions and final recommendations by categorizing chronic pain according to whether there is an identifiable or nonidentifiable cause. These chronic pain definitions were published after the release of the

guidelines outlined above. The ASH guideline panel has made new recommendations for chronic pain management that include more extensive evaluation of nonopioid pharmacological therapy (recommendations 6 and 7), nonpharmacological and integrative therapies (recommendation 8), and a tailored approach for the use of COT that balances benefit and harms (recommendation 9).

The American Pain Society published the “Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease” in 1999.¹⁹⁴ These guidelines were the first evidence-based practice guidelines for SCD pain in the United States. Many of the NHLBI SCD guidelines that focused on pain management were consensus adapted from these American Pain Society guidelines. These guidelines were not updated after their initial release 20 years ago, and therefore, they do not reflect the most recent available evidence regarding pain management in patients with SCD.

The current guidelines put forth by ASH address the role of chronic red blood cell transfusion in the management of recurrent acute and chronic pain. To our knowledge, prior guidelines did not address the role of chronic transfusions in this context. The NHLBI guidelines¹⁹³ recommended against transfusion acutely during a pain event unless there were other indications for transfusion, but the guidelines did not address the role of transfusion in the management of recurrent acute or chronic pain. The panel acknowledges that the use of chronic transfusion for pain management is likely a widespread practice that is also associated with potential risk, harm, and morbidity. Therefore, the panel felt that there was an important need to evaluate the existing evidence around the efficacy/effectiveness of chronic transfusion for the management of recurrent acute and chronic pain in this guideline development process (recommendation 10).

The Centers for Disease Control (CDC) released the “CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016.”¹⁹⁶ The target audience for these guidelines was primary care clinicians caring for adult patients with chronic pain “outside of active cancer treatment, palliative care and end-of-life care.”^{196(p1624)} Although these guidelines were not intended to pertain to patients with SCD, they were inappropriately applied to patients with SCD and thus may have affected access to opioid therapy for SCD pain management. In response to these issues, ASH addressed these concerns via a meeting and letter to the CDC asking for clarification of these guidelines.¹⁹⁷ In response, the CDC recently released a written clarification of these guidelines stating that the recommendations were not intended to apply to patients with SCD.¹⁹⁷ Recommendation 9 expands on the NHLBI guidelines and puts forth a patient-centered individualized approach for the use of COT in patients with SCD that balances benefits and harms for a given patient.

One difference between the ASH guidelines and other published guidelines is that the ASH guideline panel leveraged the extensive indirect evidence that exists for pain-related disorders other than SCD that were published as systematic reviews or meta-analyses. The process of utilizing this indirect evidence is outlined above. This evidence allowed for the development of evidence-based recommendations using the GRADE framework that are appropriately downgraded for indirectness. The NHLBI guidelines¹⁹³ used a different approach and adapted recommendations from existing general (ie, not SCD specific) chronic pain management guidelines prepared by the American Pain Society and American Academy of Pain Medicine to patients with SCD. This process resulted in

consensus-adapted recommendations. In addition, the GRADE EtD framework was not used in the NHLBI process. The application of the indirect evidence will increase awareness for interventions that may have a positive impact on treating acute and chronic SCD pain that otherwise would not have been considered. The use of nonopioid pharmacological therapy for chronic pain, including SNRIs and TCAs (recommendations 6 and 7), and use of regional anesthesia for acute pain (recommendation 2d) are such recommendations that leveraged this indirect evidence review. The use of these classes of drugs and this pain management approach were not part of the prior NHLBI guidelines for SCD pain management.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence about effects that was identified for many of the questions. There was also very limited direct evidence in individuals living with SCD upon which to base these recommendations. The majority of the direct evidence that was available included small numbers of participants and was noncomparative with a significant lack of phase 3 RCTs. Because of the paucity of direct evidence available in individuals living with SCD, the panel turned to indirect evidence to inform our recommendations. As discussed above, an iterative process was used to reach panel consensus on the questions where indirect evidence was relevant and on which pain populations this evidence would be drawn from. However, despite the panel's best efforts, it is possible that the non-SCD pain disorders/populations that were leveraged for the indirect evidence may not parallel to acute and chronic SCD pain. The process that was used to determine these populations was systematic and consensus based; however, the larger community that provides care for individuals with SCD and patients themselves may disagree with panel consensus on the relevance of these parallel populations. This potential disagreement affirms the need for further investigation into the treatment of acute and chronic pain in SCD to build a direct evidence base that can further inform the next iteration of these guidelines. In many circumstances, the level of evidence for the pediatric population is low, very low, or at times uncertain, which limited the ability of the panel to make recommendations for children and adolescents for some of the questions posed. This underscores the need for pediatric-specific investigations focused on the impact of therapies for acute and chronic SCD pain. The chronic pain guidelines are also limited in the fact that the recognition of chronic pain as a distinct entity in SCD occurred within the past decade, and therefore, the body of evidence from which to draw was not expansive. In addition, it was often difficult to delineate whether studies were evaluating the effects of interventions on acute or chronic pain. The study of pain is challenging, and the gold standard of pain assessment is self-report. Therefore, standardized self-reported assessments and outcomes are imperative. The variability in study outcomes used made it difficult to pool data across studies. Therefore, the panel concluded that validated and agreed-upon end points for SCD pain need to be established and used to be able to compare the efficacy and effectiveness of interventions for acute and chronic pain across studies. Finally, given the limited number of questions addressed by the ASH guideline panel, the prioritized questions in these guidelines may not constitute the full list of questions considered by others to be clinically important in the treatment of acute and chronic pain in SCD.

Conclusions

In conclusion, there is significant variability in the approach to pain management in individuals with SCD and a paucity of direct evidence upon which to base recommendations. Furthermore, there has been a lack of coordinated efforts to evaluate similar outcomes that are patient focused and allow comparison of effectiveness of treatments across studies. The hope is that these guidelines will provide structure around the management of acute and chronic SCD pain and identify areas of research needed that incorporate important patient-centered outcomes with the ultimate goal of decreasing pain-related suffering for individuals living with SCD. Integral to the overarching theme of these guidelines is the important need to provide individualized interdisciplinary pain management to individuals living with SCD who have acute and chronic pain, because there is no one-size-fits-all approach.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.¹⁹⁸

Acknowledgments

The authors thank Kathleen Neville and Diana Wilkie, who contributed to parts of the guideline development process;

References

1. Sil S, Cohen LL, Dampier C. Psychosocial and functional outcomes in youth with chronic sickle cell pain. *Clin J Pain*. 2016;32(6):527-533.
2. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med*. 2008;148(2):94-101.
3. Darbari DS, Ballas SK, Clauw DJ. Thinking beyond sickling to better understand pain in sickle cell disease. *Eur J Haematol*. 2014;93(2):89-95.
4. Du S, Lin C, Tao YX. Updated mechanisms underlying sickle cell disease-associated pain. *Neurosci Lett*. 2019;712:134471.
5. Tran H, Gupta M, Gupta K. Targeting novel mechanisms of pain in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2017;2017:546-555.
6. Schunemann HJ, Wiercioch W, Etzeandía I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ*. 2014;186(3):E123-E142.
7. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
8. Qaseem A, Forland F, Macbeth F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
9. Schunemann HJ, Al-Ansary LA, Forland F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548-553.
10. Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016;353:i2089.
11. Alonso-Coello P, Schunemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016.
12. Atkins D, Eccles M, Flottorp S, et al; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches the GRADE Working Group. *BMC Health Serv Res*. 2004;4:38.

M. Hassan Murad from the Mayo Clinic Evidence-Based Practice Research Program for his guidance regarding development of these guidelines and writing of the manuscript; Starr Webb and Robert Kunkle from ASH for their assistance with coordination of the guideline development effort; and Patricia Barrionuevo and other members of the Mayo team for assisting with data extraction, including Raed Benkhadra, Lubna Daraz, Magdoleen Farah, Bashar Hassan, Abdulrahman Katabi, Allison Morrow, Tarek Nayfeh, Oscar Ponte, Nigar Sofiyeva, and Zhen Wang.

Authorship

Contribution: Panel members each assisted in writing the first drafts of selected recommendations for the manuscript; A.M.B. wrote and revised the manuscript based on authors' suggestions; guideline panel members (A.M.B., C.P.C., S.C., R.E.-E., J.G., R.W.H., A.K., J.S., J.J.S., F.Y., W.Z., and E.L.) critically reviewed the manuscript and provided suggestions for improvement; a member of the systematic review team (M.S.) substantially contributed to the evidence summaries of the guidelines; all authors approved of the content; and A.M.B. and E.L. were the coauthors of the panel and led the panel meetings.

Conflict-of-interest disclosure: All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure-of-interest form, which was reviewed by ASH and is available as Supplements 2 and 3.

ORCID profiles: C.P.C., 0000-0001-7511-916X; J.J.S., 0000-0003-0341-1457; E.L., 0000-0003-0850-4337.

Correspondence: Amanda M. Brandow, Section of Hematology, Oncology, Bone Marrow Transplantation, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226; e-mail: abrandow@mcw.edu.

13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011; 64(4):383-394.
14. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
15. Schünemann HJ, Best D, Vist G, Oxman AD, Group GW. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *CMAJ*. 2003;169(7):677-680.
16. Schünemann HJ, Mustafa R, Brozek J, et al; GRADE Working Group. GRADE guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.
17. Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol*. 2016;80:3-7.
18. Dampier C, Palermo TM, Darbari DS, Hassell K, Smith W, Zempsky W. AAPT diagnostic criteria for chronic sickle cell disease pain. *J Pain*. 2017;18(5): 490-498.
19. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalgia*. 2013;33(9):629-808.
20. Lo B, Fields M. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: National Academies Press; 2009.
21. Akl EA, El-Hachem P, Abou-Haidar H, Neumann I, Schünemann HJ, Guyatt GH. Considering intellectual, in addition to financial, conflicts of interest proved important in a clinical practice guideline: a descriptive study. *J Clin Epidemiol*. 2014;67(11):1222-1228.
22. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med*. 2010;152(11): 738-741.
23. Schünemann HJ, Osborne M, Moss J, et al; ATS Ethics and Conflict of Interest Committee and the Documents Development and Implementation Committee. An official American Thoracic Society Policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med*. 2009;180(6):564-580.
24. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011; 64(4):395-400.
25. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol*. 2011;64(12):1303-1310.
26. Murad MH, Liem RI, Lang ES, et al. 2019 sickle cell disease guidelines by the American Society of Hematology: methodology, challenges, and innovations. *Blood Adv*. 2019;3(23):3945-3950.
27. Powars D, Lee S, Haywood LJ. What the emergency nurse needs to know about sickle cell disease. *J Emerg Nurs*. 1976;2(4):15-21.
28. Linehan MS. Sickle cell anemia—the painful crisis. *J Emerg Nurs*. 1978;4(6):12-19.
29. Selbst SM, Clark M. Analgesic use in the emergency department. *Ann Emerg Med*. 1990;19(9):1010-1013.
30. Belgrave FZ, Molock SD. The role of depression in hospital admissions and emergency treatment of patients with sickle cell disease. *J Natl Med Assoc*. 1991;83(9):777-781.
31. Sanders DY, Severance HW, Pollack CV Jr. Sickle cell vaso-occlusive pain crisis in adults: alternative strategies for management in the emergency department. *South Med J*. 1992;85(8):808-811.
32. Todd KH, Green C, Bonham VL Jr, Haywood C Jr, Ivy E. Sickle cell disease related pain: crisis and conflict. *J Pain*. 2006;7(7):453-458.
33. Zempsky WT. Treatment of sickle cell pain: fostering trust and justice. *JAMA*. 2009;302(22):2479-2480.
34. Zempsky WT, Loiselle KA, McKay K, Lee BH, Hagstrom JN, Schechter NL. Do children with sickle cell disease receive disparate care for pain in the emergency department? *J Emerg Med*. 2010;39(5):691-695.
35. Tanabe P, Silva S, Bosworth HB, et al. A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease (SCD). *Am J Hematol*. 2018;93(2):159-168.
36. Brandow AM, Nimmer M, Simmons T, et al. Impact of emergency department care on outcomes of acute pain events in children with sickle cell disease. *Am J Hematol*. 2016;91(12):1175-1180.
37. Patrick PA, Rosenthal BM, Iezzi CA, Brand DA. Timely pain management in the emergency department. *J Emerg Med*. 2015;48(3):267-273.
38. Kavanagh PL, Sprinz PG, Wolfgang TL, et al. Improving the management of vaso-occlusive episodes in the pediatric emergency department. *Pediatrics*. 2015;136(4):e1016-e1025.
39. Tanabe P, Reddin C, Thornton VL, Todd KH, Wun T, Lyons JS. Emergency Department Sickle Cell Assessment of Needs and Strengths (ED-SCANS), a focus group and decision support tool development project. *Acad Emerg Med*. 2010;17(8):848-858.
40. Field JJ, Ballas SK, Campbell CM, et al. AAAPT diagnostic criteria for acute sickle cell disease pain. *J Pain*. 2019;20(7):746-759.
41. Grisham JE, Vichinsky EP. Ketorolac versus meperidine in vaso-occlusive crisis: a study of safety and efficacy. *Int J Pediatr Hematol Oncol*. 1996;3: 239-247.
42. Beiter JL Jr, Simon HK, Chambliss CR, Adamkiewicz T, Sullivan K. Intravenous ketorolac in the emergency department management of sickle cell pain and predictors of its effectiveness. *Arch Pediatr Adolesc Med*. 2001;155(4):496-500.
43. Perlin E, Finke H, Castro O, et al. Enhancement of pain control with ketorolac tromethamine in patients with sickle cell vaso-occlusive crisis. *Am J Hematol*. 1994;46(1):43-47.

44. Hardwick WE Jr, Givens TG, Monroe KW, King WD, Lawley D. Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Emerg Care*. 1999;15(3):179-182.
45. Bartolucci P, El Murr T, Roudot-Thoraval F, et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. *Blood*. 2009;114(18):3742-3747.
46. Baddam S, Aban I, Hilliard L, Howard T, Askenazi D, Lebensburger JD. Acute kidney injury during a pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Nephrol*. 2017;32(8):1451-1456.
47. Griffin TC, McIntire D, Buchanan GR. High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med*. 1994;330(11):733-737.
48. Lubega FA, DeSilva MS, Munube D, et al. Low dose ketamine versus morphine for acute severe vaso occlusive pain in children: a randomized controlled trial. *Scand J Pain*. 2018;18(1):19-27.
49. Zempsky WT, Loiselle KA, Corsi JM, Hagstrom JN. Use of low-dose ketamine infusion for pediatric patients with sickle cell disease-related pain: a case series. *Clin J Pain*. 2010;26(2):163-167.
50. Tawfic QA, Faris AS, Kausalya R. The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease. *J Pain Symptom Manage*. 2014;47(2):334-340.
51. Gimovsky AC, Fritton K, Viscusi E, Roman A. Evaluating the use of ketamine for pain control with sickle cell crisis in pregnancy: a report of 2 cases. *A A Pract*. 2018;10(1):20-22.
52. Sheehy KA, Lippold C, Rice AL, Nobrega R, Finkel JC, Quezada ZMN. Subanesthetic ketamine for pain management in hospitalized children, adolescents, and young adults: a single-center cohort study. *J Pain Res*. 2017;10:787-795.
53. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):456-466.
54. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):521-546.
55. New T, Venable C, Fraser L, et al. Management of refractory pain in hospitalized adolescents with sickle cell disease: changing from intravenous opioids to continuous infusion epidural analgesia. *J Pediatr Hematol Oncol*. 2014;36(6):e398-e402.
56. Yaster M, Tobin JR, Billett C, Casella JF, Dover G. Epidural analgesia in the management of severe vaso-occlusive sickle cell crisis. *Pediatrics*. 1994;93(2):310-315.
57. Abou-Setta AM, Beaupre LA, Rashiq S, et al. Comparative effectiveness of pain management interventions for hip fracture: a systematic review. *Ann Intern Med*. 2011;155(4):234-245.
58. Anim-Somuah M, Smyth RM, Cyna AM, Cuthbert A. Epidural versus non-epidural or no analgesia for pain management in labour. *Cochrane Database Syst Rev*. 2018;5:CD000331.
59. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA*. 2003;290(18):2455-2463.
60. Okpala I. The management of crisis in sickle cell disease. *Eur J Haematol*. 1998;60(1):1-6.
61. Carden MA, Patil P, Ahmad ME, Lam WA, Joiner CH, Morris CR. Variations in pediatric emergency medicine physician practices for intravenous fluid management in children with sickle cell disease and vaso-occlusive pain: a single institution experience. *Pediatr Blood Cancer*. 2018;65(1):e26742.
62. Okomo U, Meremikwu MM. Fluid replacement therapy for acute episodes of pain in people with sickle cell disease. *Cochrane Database Syst Rev*. 2017;7:CD005406.
63. Moody K, Abrahams B, Baker R, et al. A randomized trial of yoga for children hospitalized with sickle cell vaso-occlusive crisis. *J Pain Symptom Manage*. 2017;53(6):1026-1034.
64. Co LL, Schmitz TH, Havdala H, Reyes A, Westerman MP. Acupuncture: an evaluation in the painful crises of sickle cell anaemia. *Pain*. 1979;7(2):181-185.
65. Wang WC, George SL, Wilimas JA. Transcutaneous electrical nerve stimulation treatment of sickle cell pain crises. *Acta Haematol*. 1988;80(2):99-102.
66. Lu K, Cheng MC, Ge X, et al. A retrospective review of acupuncture use for the treatment of pain in sickle cell disease patients: descriptive analysis from a single institution. *Clin J Pain*. 2014;30(9):825-830.
67. Lemaneck KL, Ranalli M, Lukens C. A randomized controlled trial of massage therapy in children with sickle cell disease. *J Pediatr Psychol*. 2009;34(10):1091-1096.
68. Dobson CE, Byrne MW. Original research: using guided imagery to manage pain in young children with sickle cell disease. *Am J Nurs*. 2014;114(4):26-36; test 37, 47.
69. Ezenwa MO, Yao Y, Engeland CG, et al. A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *J Adv Nurs*. 2016;72(6):1452-1463.
70. Thomas JE, Koshy M, Patterson L, Dorn L, Thomas K. Management of pain in sickle cell disease using biofeedback therapy: a preliminary study. *Biofeedback Self Regul*. 1984;9(4):413-420.

71. Agrawal AK, Robertson S, Litwin L, et al. Virtual reality as complementary pain therapy in hospitalized patients with sickle cell disease. *Pediatr Blood Cancer*. 2019;66(2):e27525.
72. Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: a systematic review. *Clin Psychol Rev*. 2010;30(8):1011-1018.
73. Wittkopf PG, Lloyd DM, Johnson MI. Managing limb pain using virtual reality: a systematic review of clinical and experimental studies. *Disabil Rehabil*. 2019;41(26):3103-3117.
74. Chan E, Foster S, Sambell R, Leong P. Clinical efficacy of virtual reality for acute procedural pain management: a systematic review and meta-analysis. *PLoS One*. 2018;13(7):e0200987.
75. Shahrbanian S, Ma X, Korner-Bitensky N, Simmonds MJ. Scientific evidence for the effectiveness of virtual reality for pain reduction in adults with acute or chronic pain. *Stud Health Technol Inform*. 2009;144:40-43.
76. Boitor M, Gelinas C, Richard-Lalonde M, Thombs BD. The effect of massage on acute postoperative pain in critically and acutely ill adults post-thoracic surgery: systematic review and meta-analysis of randomized controlled trials. *Heart Lung*. 2017;46(5):339-346.
77. Sbruzzi G, Silveira SA, Silva DV, Coronel CC, Plentz RD. Transcutaneous electrical nerve stimulation after thoracic surgery: systematic review and meta-analysis of 11 randomized trials [in English, Portuguese]. *Rev Bras Cir Cardiovasc*. 2012;27(1):75-87.
78. Li J, Song Y. Transcutaneous electrical nerve stimulation for postoperative pain control after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96(37):e8036.
79. Wu MS, Chen KH, Chen IF, et al. The efficacy of acupuncture in post-operative pain management: a systematic review and meta-analysis. *PLoS One*. 2016;11(3):e0150367.
80. Koch KL, Karafin MS, Simpson P, Field JJ. Intensive management of high-utilizing adults with sickle cell disease lowers admissions. *Am J Hematol*. 2015;90(3):215-219.
81. 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. *Am J Hematol*. 2015;90(5):376-380.
82. Molokie RE, Montminy C, Dionisio C, et al. Opioid doses and acute care utilization outcomes for adults with sickle cell disease: ED versus acute care unit. *Am J Emerg Med*. 2018;36(1):88-92.
83. Raphael JL, Kamdar A, Beavers MB, Mahoney DH, Mueller BU. Treatment of uncomplicated vaso-occlusive crises in children with sickle cell disease in a day hospital. *Pediatr Blood Cancer*. 2008;51(1):82-85.
84. Benjamin LJ, Swinson GI, Nagel RL. Sickle cell anemia day hospital: an approach for the management of uncomplicated painful crises. *Blood*. 2000;95(4):1130-1136.
85. Wright J, Bareford D, Wright C, et al. Day case management of sickle pain: 3 years experience in a UK sickle cell unit. *Br J Haematol*. 2004;126(6):878-880.
86. Adewoye AH, Nolan V, McMahon L, Ma Q, Steinberg MH. Effectiveness of a dedicated day hospital for management of acute sickle cell pain. *Haematologica*. 2007;92(6):854-855.
87. Augier R, Jenkins S, Bortolusso Ali S, Tennant I, Williams-Johnson J, Reid M. A survey of the pain management of acute painful crisis among patients with sickle cell disease at two centres in Jamaica. *West Indian Med J*. 2014;63(3):252-257.
88. Binding A, Ward R, Phua C, et al. An innovative short-stay health care model for treatment of uncomplicated vaso-occlusive crisis in adult sickle cell disease patients in Canada to reduce emergency department utilization. *CJEM*. 2019;21(1):55-62.
89. Dampier CD, Smith WR, Wager CG, et al; Sickle Cell Disease Clinical Research Network (SCDCRN). IMPROVE trial: a randomized controlled trial of patient-controlled analgesia for sickle cell painful episodes: rationale, design challenges, initial experience, and recommendations for future studies. *Clin Trials*. 2013;10(2):319-331.
90. George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. *J Opioid Manag*. 2010;6(1):47-54.
91. Hayes J, Dowling JJ, Peliowski A, Crawford MW, Johnston B. Patient-controlled analgesia plus background opioid infusion for postoperative pain in children: a systematic review and meta-analysis of randomized trials. *Anesth Analg*. 2016;123(4):991-1003.
92. Horlocker TT, Burton AW, Connis RT, et al; American Society of Anesthesiologists Task Force on Neuraxial Opioids. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology*. 2009;110(2):218-230.
93. Delaney KM, Axelrod KC, Buscetta A, et al. Leg ulcers in sickle cell disease: current patterns and practices. *Hemoglobin*. 2013;37(4):325-332.
94. Blinder MA, Russel S, Barnes M. Prevalence of symptomatic avascular necrosis and the operative treatment in adult patients with sickle cell disease [abstract]. *Blood*. 2014;124(21). Abstract 1379.
95. Brandalise SR, Assis R, Laranjeira ABA, Yunes JA, de Campos-Lima PO. Low-dose methotrexate in sickle-cell disease: a pilot study with rationale borrowed from rheumatoid arthritis. *Exp Hematol Oncol*. 2017;6:18.
96. Odebiyi DO, Adigun OT, Kehinde MO. Effect of sodium salicylate iontophoresis in the management of hip pain in patients with sickle cell disease. *Nig Q J Hosp Med*. 2007;17(2):82-86.
97. Cacciola E, Giustolisi R, Musso R, Longo A, Cacciola E. Antithrombin III concentrate for treatment of chronic leg ulcers in sickle cell-beta thalassemia: a pilot study. *Ann Intern Med*. 1989;111(6):534-536.
98. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? *Postgrad Med*. 2012;124(1):83-93.

99. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. *Pain Med*. 2015;16(7):1373-1385.
100. Myers J, Wielage RC, Han B, et al. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. *BMC Musculoskelet Disord*. 2014;15:76.
101. MacKay C, Clements N, Wong R, Davis AM. A systematic review of estimates of the minimal clinically important difference and patient acceptable symptom state of the Western Ontario and McMaster Universities Osteoarthritis Index in patients who underwent total hip and total knee replacement. *Osteoarthritis Cartilage*. 2019;27(10):1408-1419.
102. Xu C, Gu K, Yasen Y, Hou Y. Efficacy and safety of celecoxib therapy in osteoarthritis: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2016;95(20):e3585.
103. Zou K, Wong J, Abdullah N, et al. Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2016;75(11):1964-1970.
104. Jung SY, Jang EJ, Nam SW, et al. Comparative effectiveness of oral pharmacologic interventions for knee osteoarthritis: a network meta-analysis. *Mod Rheumatol*. 2018;28(6):1021-1028.
105. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21-e33.
106. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54.
107. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225.
108. Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthritis Cartilage*. 2016;24(6):962-972.
109. Gregori D, Giacobelli G, Minto C, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA*. 2018;320(24):2564-2579.
110. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ*. 2004;329(7461):324.
111. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683-1696.
112. Weir MR. Renal effects of nonselective NSAIDs and coxibs. *Cleve Clin J Med*. 2002;69(suppl 1):SI53-SI58.
113. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1994;331(25):1675-1679.
114. Nelson DA, Marks ES, Deuster PA, O'Connor FG, Kurina LM. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA Netw Open*. 2019;2(2):e187896.
115. Haag MD, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. *Arch Intern Med*. 2008;168(11):1219-1224.
116. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010;62(6):1592-1601.
117. Osunkwo I, Ziegler TR, Alvarez J, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. *Br J Haematol*. 2012;159(2):211-215.
118. Schlaeger JM, Molokie RE, Yao Y, et al. Management of sickle cell pain using pregabalin: a pilot study. *Pain Manag Nurs*. 2017;18(6):391-400.
119. Jerrell JM, Tripathi A, Stallworth JR. Pain management in children and adolescents with sickle cell disease. *Am J Hematol*. 2011;86(1):82-84.
120. Cooper TE, Wiffen PJ, Heathcote LC, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;8(8):CD012536.
121. Häuser W, Urrútia G, Tort S, Uçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2013;(1):CD010292.
122. Häuser W, Wolfe F, Tölle T, Uçeyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs*. 2012;26(4):297-307.
123. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. *Cochrane Database Syst Rev*. 2016;9:CD011790.
124. Arnold LM, Schikler KN, Bateman L, et al; Pregabalin Adolescent Fibromyalgia Study Group. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. *Pediatr Rheumatol Online J*. 2016;14(1):46.
125. US Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. Available at: <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications>. Accessed 12 August 2019.
126. Schatz J, Schlenz AM, McClellan CB, et al. Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *Clin J Pain*. 2015;31(6):536-547.

127. Barakat LP, Schwartz LA, Salamon KS, Radcliffe J. A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *J Pediatr Hematol Oncol*. 2010;32(7):540-547.
128. Thomas VJ, Dixon AL, Milligan P, Thomas N. Cognitive-behaviour therapy for the management of sickle cell disease pain: an evaluation of a community-based intervention. *Br J Health Psychol*. 1999;4(3):209-229.
129. Gil KM, Carson JW, Sedway JA, Porter LS, Schaeffer JJ, Orringer E. Follow-up of coping skills training in adults with sickle cell disease: analysis of daily pain and coping practice diaries. *Health Psychol*. 2000;19(1):85-90.
130. Dobson C. Outcome results of self-efficacy in children with sickle disease pain who were trained to use guided imagery. *Appl Nurs Res*. 2015;28(4):384-390.
131. Dinges DF, Whitehouse WG, Orne EC, et al. Self-hypnosis training as an adjunctive treatment in the management of pain associated with sickle cell disease. *Int J Clin Exp Hypn*. 1997;45(4):417-432.
132. Myrvik MP, Campbell AD, Butcher JL. Single-session biofeedback-assisted relaxation training in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2012;34(5):340-343.
133. Matheve T, Brumagne S, Timmermans AAA. The effectiveness of technology-supported exercise therapy for low back pain: a systematic review. *Am J Phys Med Rehabil*. 2017;96(5):347-356.
134. Richmond H, Hall AM, Copsey B, et al. The effectiveness of cognitive behavioural treatment for non-specific low back pain: a systematic review and meta-analysis. *PLoS One*. 2015;10(8):e0134192.
135. Bernardy K, Füber N, Köllner V, Häuser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol*. 2010;37(10):1991-2005.
136. Bawa FL, Mercer SW, Atherton RJ, et al. Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. *Br J Gen Pract*. 2015;65(635):e387-e400.
137. Sielski R, Rief W, Glombiewski JA. Efficacy of biofeedback in chronic back pain: a meta-analysis. *Int J Behav Med*. 2017;24(1):25-41.
138. Myers CD, Robinson ME, Guthrie TH, Lamp SP, Lottenberg R. Adjunctive approaches for sickle cell chronic pain. *Altern Health Pract*. 1999;5:203-212.
139. Cozzi L, Tryon WW, Sedlacek K. The effectiveness of biofeedback-assisted relaxation in modifying sickle cell crises. *Biofeedback Self Regul*. 1987;12(1):51-61.
140. Li YH, Wang FY, Feng CQ, Yang XF, Sun YH. Massage therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9(2):e89304.
141. Rubinstein SM, van Middelkoop M, Kuijpers T, et al. A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. *Eur Spine J*. 2010;19(8):1213-1228.
142. Yuan QL, Guo TM, Liu L, Sun F, Zhang YG. Traditional Chinese medicine for neck pain and low back pain: a systematic review and meta-analysis. *PLoS One*. 2015;10(2):e0117146.
143. Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for low back pain: a systematic review. *Spine*. 2008;33(23):E887-E900.
144. Lam M, Galvin R, Curry P. Effectiveness of acupuncture for nonspecific chronic low back pain: a systematic review and meta-analysis. *Spine*. 2013;38(24):2124-2138.
145. Wells C, Kolt GS, Marshall P, Hill B, Bialocerkowski A. The effectiveness of Pilates exercise in people with chronic low back pain: a systematic review. *PLoS One*. 2014;9(7):e100402.
146. Bidonde J, Busch AJ, Bath B, Milosavljevic S. Exercise for adults with fibromyalgia: an umbrella systematic review with synthesis of best evidence. *Curr Rheumatol Rev*. 2014;10(1):45-79.
147. Häuser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2010;12(3):R79.
148. Searle A, Spink M, Ho A, Chuter V. Exercise interventions for the treatment of chronic low back pain: a systematic review and meta-analysis of randomised controlled trials. *Clin Rehabil*. 2015;29(12):1155-1167.
149. van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J*. 2011;20(1):19-39.
150. Macedo LG, Maher CG, Latimer J, McAuley JH. Motor control exercise for persistent, nonspecific low back pain: a systematic review. *Phys Ther*. 2009;89(1):9-25.
151. Smith BE, Littlewood C, May S. An update of stabilisation exercises for low back pain: a systematic review with meta-analysis. *BMC Musculoskelet Disord*. 2014;15:416.
152. Wang XQ, Zheng JJ, Yu ZW, et al. A meta-analysis of core stability exercise versus general exercise for chronic low back pain. *PLoS One*. 2012;7(12):e52082.
153. Von Korff M, Dublin S, Walker RL, et al. The impact of opioid risk reduction initiatives on high-dose opioid prescribing for patients on chronic opioid therapy. *J Pain*. 2016;17(1):101-110.
154. Turner JA, Shortreed SM, Saunders KW, LeResche L, Thielke S, Von Korff M. Does association of opioid use with pain and function differ by fibromyalgia or widespread pain status? *Pain*. 2016;157(10):2208-2216.
155. Els C, Jackson TD, Hagtvædt R, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;10(10):CD012299.

156. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA*. 2018;320(23):2448-2460.
157. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4):276-286.
158. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;2010(1):CD006605.
159. Cooper TE, Fisher E, Gray AL, et al. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;7(7):CD012538.
160. Gulur P, Williams L, Chaudhary S, Koury K, Jaff M. Opioid tolerance—a predictor of increased length of stay and higher readmission rates. *Pain Physician*. 2014;17(4):E503-E507.
161. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med*. 2013;173(3):196-201.
162. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med*. 2013;273(5):511-526.
163. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of fracture in adults: a nested case-control study using the general practice research database. *Am J Epidemiol*. 2013;178(4):559-569.
164. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine*. 2013;38(11):909-915.
165. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.
166. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686-691.
167. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*. 2014;30(7):557-564.
168. Ruta NS, Ballas SK. The opioid drug epidemic and sickle cell disease: guilt by association. *Pain Med*. 2016;17(10):1793-1798.
169. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality [published correction appears in *Pain Med*. 2016;17(4):797-798]. *Pain Med*. 2016;17(1):85-98.
170. Murphy L, Babaei-Rad R, Buna D, et al. Guidance on opioid tapering in the context of chronic pain: evidence, practical advice and frequently asked questions. *Can Pharm J*. 2018;151(2):114-120.
171. Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med*. 2018;178(5):707-708.
172. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription opioid taper support for outpatients with chronic pain: a randomized controlled trial. *J Pain*. 2017;18(3):308-318.
173. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. *Mayo Clin Proc*. 2015;90(6):828-842.
174. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. 2013;29(2):109-117.
175. Haroutianian S, Donaldson G, Yu J, Lipman AG. Development and validation of shortened, restructured Treatment Outcomes in Pain Survey instrument (the S-TOPS) for assessment of individual pain patients' health-related quality of life. *Pain*. 2012;153(8):1593-1601.
176. HealthMeasures. Pain domains. Available at: <http://www.healthmeasures.net/search-view-measures?task=Search.search>. Accessed 1 September 2019.
177. Black RA, McCaffrey SA, Villapiano AJ, Jamison RN, Butler SF. Development and validation of an eight-item brief form of the SOAPP-R (SOAPP-8). *Pain Med*. 2018;19(10):1982-1987.
178. McCaffrey SA, Black RA, Villapiano AJ, Jamison RN, Butler SF. Development of a brief version of the Current Opioid Misuse Measure (COMM): the COMM-9. *Pain Med*. 2019;20(1):113-118.
179. Jamison RN, Martel MO, Huang CC, Jurcik D, Edwards RR. Efficacy of the opioid compliance checklist to monitor chronic pain patients receiving opioid therapy in primary care. *J Pain*. 2016;17(4):414-423.
180. Jamison RN, Edwards RR. Risk factor assessment for problematic use of opioids for chronic pain. *Clin Neuropsychol*. 2013;27(1):60-80.
181. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse (part 2). *Pain Physician*. 2017;20(2S):S111-S133.
182. Charache S, Terrin ML, Moore RD, et al; Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332(20):1317-1322.
183. Niihara Y, Miller ST, Kanter J, et al; Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease. A phase 3 trial of L-glutamine in sickle cell disease. *N Engl J Med*. 2018;379(3):226-235.
184. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-439.
185. National Heart, Lung, and Blood Institute Expert Panel. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report 2014. Bethesda, MD: National Institutes of Health; 2014.
186. Alvarez O, Yovetich NA, Scott JP, et al; Investigators of the Stroke With Transfusions Changing to Hydroxyurea Clinical Trial (SWITCH). Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: results from the SWITCH clinical trial. *Am J Hematol*. 2013;88(11):932-938.

187. Kalf A, Dowsing C, Grigg A. The impact of a regular erythrocytapheresis programme on the acute and chronic complications of sickle cell disease in adults. *Br J Haematol*. 2010;149(5):768-774.
188. Koshy M, Burd L, Wallace D, Moawad A, Baron J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *N Engl J Med*. 1988;319(22):1447-1452.
189. DeBaun MR, Gordon M, McKinsty RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;371(8):699-710.
190. Miller ST, Wright E, Abboud M, et al; STOP Investigators. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. *J Pediatr*. 2001;139(6):785-789.
191. Hilliard LM, Kulkarni V, Sen B, et al. Red blood cell transfusion therapy for sickle cell patients with frequent painful events. *Pediatr Blood Cancer*. 2018;65(12):e27423.
192. Styles LA, Vichinsky E. Effects of a long-term transfusion regimen on sickle cell-related illnesses. *J Pediatr*. 1994;125(6 pt 1):909-911.
193. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members [published corrections appear in *JAMA*. 2014;312(18):1932, *JAMA*. 2015;313(7):729]. *JAMA*. 2014;312(10):1033-1048.
194. Benjamin LJ, Dampier CD, Jacox AK, et al. Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease. Glenview, IL: American Pain Society; 1999.
195. Center for Clinical Practice at NICE. *Sickle Cell Acute Painful Episode: Management of an Acute Painful Sickle Cell Episode in Hospital*. Manchester, United Kingdom: National Institute for Health and Clinical Excellence. 2012.
196. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645.
197. American Society of Hematology. CDC issues key clarification on guideline for prescribing opioids for chronic pain. <https://hematology.org/newsroom/press-releases/2019/cdc-issues-key-clarification-guideline-prescribing-opioids-chronic-pain>. Accessed 10 September 2019.
198. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. 2017;81:101-110.