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Focus Article

AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain



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Abstract: Pain in sickle cell disease (SCD) is associated with increased morbidity, mortality, and high health care costs. Although episodic acute pain is the hallmark of this disorder, there is an increasing awareness that chronic pain is part of the pain experience of many older adolescents and adults. A common set of criteria for classifying chronic pain associated with SCD would enhance SCD pain research efforts in epidemiology, pain mechanisms, and clinical trials of pain management interventions, and ultimately improve clinical assessment and management. As part of the collaborative effort between the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative developed the outline of an optimal diagnostic system for chronic pain conditions. Subsequently, a working group of experts in SCD pain was convened to generate core diagnostic criteria for chronic pain associated with SCD. The working group synthesized available literature to provide evidence for the dimensions of this disease-specific pain taxonomy. A single pain condition labeled chronic SCD pain was derived with 3 modifiers reflecting different clinical features. Future systematic research is needed to evaluate the feasibility, validity, and reliability of these criteria.

Perspective: An evidence-based classification system for chronic SCD pain was constructed for the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative. Applying this taxonomy may improve assessment and management of SCD pain and accelerate research on epidemiology, mechanisms, and treatments for chronic SCD pain.

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Key words: Sickle cell disease, chronic pain, taxonomy, diagnostic criteria.

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Sickle cell disease (SCD) encompasses a group of related genetic disorders of hemoglobin structure, and is the most common genetic blood disease among individuals in North America. SCD most commonly occurs in individuals whose ethnic origin is from Africa, Middle East, Indian Subcontinent, Southern Europe, South or Central America, or the Caribbean.³⁵ The hallmark feature of SCD is recurrent episodes of acute pain, presumably ischemic in origin, caused by a remarkably complex process leading to obstruction of blood flow in vulnerable tissue beds by sickled erythrocytes,⁷² typically referred to as a vaso-occlusive crisis.⁶³ From the patient perspective, SCD pain is reportedly worse than postoperative pain,^{16,32} as intense as cancer pain,⁸² and has a negative effect on all aspects of the individual's health-related quality of life.^{21,22} Recurrent pain is the main reason for SCD-related hospitalization, and drives annual health care costs of \$1.1 billion.⁴² Having frequent or prolonged episodes of pain is a key predictor of morbidity and mortality.^{38,60,61} Although as yet poorly studied, clinicians and researchers are increasingly appreciating that for many adolescent and adult patients with SCD these episodes of recurrent acute pain occur in the context of ongoing persistent or chronic pain.^{13,69}

Mounting evidence shows that the burden of SCD pain as well as pain-associated health care utilization increase from childhood to adolescence and young adulthood.^{19,67,69,70} Diary studies show that children with SCD report pain on 16 to 30% of days and pain becomes more severe in adolescence as evidenced by a marked increase in the use of opioids (57% of days in youth ages 14–19 years old, but only 10–11% of days in younger age groups).^{19,67} By adulthood, the prevalence of pain continues to increase. For example, in the Pain in Sickle Cell Epidemiology Study, a daily diary study of 232 adults with SCD, 55% of adult respondents reported pain on more than half of the days and 29% reported pain on 95% of days, suggesting a substantial prevalence of chronic pain.⁶⁹ Whereas most of these reported pain days were not described as “crisis” pain, a minority of pain days with more intense pain were described as “crisis”-related. The temporal overlap of these “crisis” and non-“crisis” pain days suggested some individuals experienced a pattern of acute episodic pain superimposed upon chronic pain.

Consistent with other pediatric chronic pain conditions, youth with SCD reporting pain on most days had significantly greater functional disability, depressive symptoms, and inpatient admissions for pain relative to patients characterized as having episodic or no SCD pain.⁶⁸ Similarly, adults with frequent days of pain had higher somatic symptom burden and were more likely to be depressed or anxious.⁷¹

There are no existing consensus-based criteria for chronic SCD pain from which to draw for deriving a formal diagnostic classification. This lack of clarity in what defines chronic SCD pain has hindered research efforts in understanding the epidemiology of chronic SCD pain, mechanisms of chronic SCD pain, and in developing effective pain management interventions in this

population. Chronic pain criteria on the basis of the duration of pain persistence from an inciting event, such as used for postoperative pain, is particularly problematic in a condition like SCD in which patterns of frequent recurrent pain occur. The likely overlap of acute and chronic pain suggested the potential utility of a frequency-based criteria similar to the classification system of the International Classification of Headache Disorders,³⁶ because of the similar episodic nature of headache disorders compared with acute sickle pain and the propensity for frequent headaches to become chronic or daily.

To meet the need for an evidence-based chronic pain classification system, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society collaborated to develop the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT). The resultant pain taxonomy framework developed through this initiative incorporates knowledge of biopsychosocial mechanisms and classifies chronic pain conditions along 5 dimensions including: 1) core diagnostic criteria, 2) common features, 3) common medical and psychiatric comorbidities, 4) neurobiological, psychological, and functional consequences, and 5) putative neurobiological and psychosocial mechanisms, risk factors, and protective factors. This framework is comprehensively described in Fillingim et al³⁰ and further background concerning the AAPT initiative is available in a series of additional review articles.^{10,27,29,31,48,75,78,80}

The aim of our working group on SCD pain was to apply the AAPT framework to identify chronic pain condition(s) associated with SCD and to propose a diagnostic classification system on the basis of the 5 dimensions of the AAPT.

Methods

A 6-member interdisciplinary work group (WG) of clinicians and clinical scientists with expertise in SCD pain and chronic pain across the lifespan was convened. The WGs met during an AAPT consensus conference in July 2014 in Annapolis, Maryland. Before the meeting, relevant guidelines and literature on SCD pain was searched and compiled to examine pain definitions, epidemiology, and risk factors. In particular, key review articles proposing definitions or conceptualizations of chronic SCD pain were identified (eg, Ballas,⁴ Ballas et al,⁵ and Taylor et al⁷³), and original research presenting data on pain patterns and characteristics available from daily diary studies in the SCD population were reviewed.⁶⁹ In several teleconferences before the meeting, this literature was discussed and preliminary definitions of chronic SCD pain were drafted.

The WG made the decision to not perform an exhaustive review of the literature. Systematic reviews conducted recently to inform the 2014 evidence-based report on management of SCD⁸⁴ reported little evidence related

specifically to chronic pain of individuals with SCD. Thus, the WG's stance was that proposing another systematic review was not anticipated to yield new findings. Rather, the WG sought to identify key definitions, focusing discussion on significant items pertaining to defining chronic pain in SCD. Background readings provided by the AAPT steering committee relating to multiaxial diagnostic classification systems were also reviewed so that the WG could apply this evidence-based framework to chronic pain in SCD.

During the consensus conference, full details on the AAPT framework were presented by the steering committee, and the WG developed an initial draft version that contained 2 diagnostic categories for chronic SCD pain. Each chronic pain WG presented their draft diagnostic categories to the larger group allowing for additional opportunities to incorporate feedback to refine signs and symptoms proposed in the classification system.

After the consensus meeting, the WG used the AAPT background documents and conducted several teleconferences to further refine the draft diagnostic categories. The WG coauthors (C.D. and T.M.P.) compiled literature to support the diagnostic categories proposed. Because of the lack of available evidence from the literature specifically on chronic pain in SCD to support 2 distinct diagnoses of chronic SCD pain, the WG members unanimously

agreed to revise the draft categories to instead propose a single diagnostic category of chronic SCD pain. In line with the evidence-based recommendations for managing chronic complications of SCD⁸⁴ the WG proposed 3 subtypes of chronic SCD pain to account for the effect of chronic complications of SCD on the experience of chronic pain. The AAPT steering committee provided the structure for Table 1 and suggested terminology for all WGs to apply. Revisions were made until all WG members agreed on the wording of each of the signs and symptoms listed.

Results

Our proposed classification is for a single pain condition, which we label chronic SCD pain, with 3 subtypes: 1) chronic SCD pain without contributory disease complications, 2) chronic SCD pain with contributory disease complications, and 3) chronic SCD pain with mixed presentation.

Chronic SCD Pain

Dimension 1. Core Diagnostic Criteria of Chronic SCD Pain

The AAPT criteria for chronic SCD pain are summarized in Table 1. The history must include a diagnosis of SCD confirmed by appropriate laboratory testing. Three diagnostic modifiers indicate subtypes of chronic SCD pain to distinguish between the presence or absence of contributory disease complications as a source of chronic pain (eg, leg ulcers, avascular necrosis) and a mixed presentation that includes pain in the presence of local contributory disease complications as well as pain also occurring in other unrelated sites. Differential diagnosis includes distinguishing between chronic SCD pain and other primary pain conditions with specific defined etiologies that individuals with SCD may develop, such as migraine headaches or autoimmune disorders (eg, lupus, rheumatoid arthritis).^{39,55,56} Previous research has shown that patients are able to attribute pain to their SCD rather than to other causes (eg, other injuries or illnesses) and to distinguish crisis pain from noncrisis pain (presumably ongoing chronic pain).^{19,69,82}

Diagnosis of chronic SCD pain requires that, in addition to ongoing pain, the patient displays at least 1 sign of pain sensitivity on palpation or with movement of the region of reported pain, decreased range of motion or weakness in the region of reported pain, or evidence of chronic disease complications (eg, skin ulcer, splenic infarct, or bone infarction) associated with the region of reported pain.

Dimension 2. Common Features of Chronic SCD Pain, Including Epidemiology and Lifespan Considerations

SCD pain is considered to be chronic SCD pain when such pain is present on most days, and has occurred for at least the previous 6 months. As noted, more than half of adult patients with SCD report pain on more than half of days,

Table 1. AAPT Diagnostic Criteria for Chronic Pain Associated With SCD (Chronic SCD Pain)

DIMENSION 1: CORE DIAGNOSTIC CRITERIA

1. Diagnosis of SCD confirmed by laboratory testing
2. Reports of ongoing pain present on most days over the past 6 months either in a single location or in multiple locations
3. Must display at least 1 sign:
 - Palpation of the region of reported pain elicits focal pain or tenderness
 - Movement of the region of reported pain elicits focal pain
 - Decreased range of motion or weakness in the region of reported pain
 - Evidence of skin ulcer in the region of reported pain
 - Evidence of hepatobiliary or splenic imaging abnormalities (eg, splenic infarct, chronic pancreatitis) consistent with the region of reported pain
 - Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain
4. There is no other diagnosis that better explains the signs and symptoms

Chronic SCD pain diagnostic modifiers:

We propose 3 diagnostic modifiers to indicate subtypes of chronic SCD pain.

1. Chronic SCD pain without contributory disease complications is used if there is no evidence of contributory SCD complications on the basis of either clinical signs (eg, presence of leg ulcers) or test results (eg, imaging abnormalities)
2. Chronic SCD pain with contributory disease complications should be used if there is evidence of contributory SCD complications on the basis of clinical signs or test results
3. Chronic SCD pain with mixed pain types should be used if there is evidence of contributory SCD complications (eg, avascular necrosis) on the basis of clinical signs or test results and there is pain also occurring in unrelated sites (eg, arms, back, chest, or abdominal pain)

and 29% report pain occurring almost daily.⁶⁹ Similarly, 15% of adolescents, and 10% of young children with SCD also report pain on most days lasting greater than 6 months.⁶⁸ The daily use of opioids for pain management in older children and adolescents, and in adults, is also reported, consistent with reports of very frequent or daily pain.^{17,67} Pain in multiple locations is common^{20,32} with an average of 3 or more sites of pain identified by patients,⁵⁰ most commonly extremities, back, and abdominal sites. Most patients describe their pain as constant, continuous, or steady.⁸² Half of patients also describe/report pain patterns that are intermittent, periodic, or rhythmic.^{69,82} In one study, 90% of 145 adults with SCD described their pain using at least some neuropathic pain descriptors on a pain quality questionnaire.⁸² Unfortunately, only a few of these studies distinguished between acute and chronic pain, so additional data are needed to identify features unique to chronic SCD pain. Compared with those with infrequent episodic pain, children and adolescents with chronic SCD pain were seen more often for pain management in acute care and hospital settings, reflecting the difficulties of treating combined acute and chronic pain.⁶⁶

Individuals with SCD may experience pain originating from complications in bone or associated structures, soft tissues, and internal organs. Hepatic or splenic enlargement from accumulation of fluid and blood cells may lead to chronic pain from capsular stretch or pericapsular infarction. Other pain symptoms related to disease complications include pain at the site of ulcers that occur in the skin and associated soft tissues on either side of the ankles,⁵³ and pain at the site of the humeral or femoral heads from avascular necrosis.^{51,66} Although uncommon in children, prevalence rates for leg ulcers in adults with SCD range from 5 to 10%.⁴³ Avascular necrosis can occur in older children, adolescents, and adults in either the hip (femoral head) or shoulder (humeral head) joint and is often bilateral (40–60%).^{1,47} The co-occurrence of shoulder and hip involvement is also high. Similarly, persistent back pain from vertebral collapse or fractures occurs in 2 to 5% of individuals with SCD.⁶⁵ These SCD complications create persistent or irreversible injury and contribute to significant pain. For example, in a study of adults with SCD, ulcers had been present for a median of 10 months with a range of 2 to 300 months.⁵²

Dimension 3. Common Medical and Psychiatric Comorbidities Associated With Chronic SCD Pain

Clinical manifestations of SCD vary by frequency and severity and are hypothesized to have differing pathophysiology. Natural history studies suggest that more frequent acute vaso-occlusive pain and certain disease characteristics (eg, presence of alpha thalassemia characterized by higher hematocrit, lower mean corpuscular volume) are associated with osteonecrosis of the femoral head.⁵¹ In contrast, other disease complications such as leg ulcers are more strongly associated with intensity of hemolysis⁴¹ than with frequency of acute vaso-

occlusive pain. Frequent acute pain has also been associated with an increased risk of pulmonary hypertension and subsequent cardiovascular disease,²⁵ and with an increased risk for acute chest syndrome and subsequent chronic pulmonary disorders.^{59,77} Asthma has been associated with an increased frequency of acute pain and chest syndrome episodes.²⁶ Similar to other chronic pain conditions,²⁹ chronic SCD pain is also associated with comorbid psychiatric illness, most commonly major depression and anxiety disorders.^{40,44,73,83}

Dimension 4. Neurobiological, Psychosocial, and Functional Consequences of Chronic SCD Pain

Although not well characterized, the consequences of chronic SCD pain likely include common psychosocial and functional effects experienced by individuals with other types of chronic pain, which are summarized in Turk et al.⁷⁵ In children and adolescents, acute SCD pain is associated with increased impairment in daily activities such as school,^{28,64} having fewer friends, and being less physically active.²² Reductions in health-related quality of life are well documented in adults²¹ and children with SCD pain, some of which was likely chronic SCD pain.⁵⁸ Activity restrictions because of persistent pain are common in almost all chronic pain disorders.⁴⁵ Fatigue,² somatic symptoms,⁷¹ and sleep disturbances (including behavioral sleep problems, sleep fragmentation, and increased risk for sleep disordered breathing and periodic limb movements^{46,76}) are common and associated with increased pain-related disability in SCD adults, many of whom likely had chronic SCD pain. For example, in one study of 328 adults with SCD, more than 70% had sleep disturbances, which were more common among those adults with frequent SCD pain.⁸¹

Studies have shown that SCD disease complications are associated with similar effects on function. Children and adolescents with hip avascular necrosis have reduced physical function of the affected hip^{1,18} and parents report diminished global physical functioning.²² Similarly, adults with pain due to either hip avascular necrosis or leg ulcers report effects on their physical functioning.²¹

Because SCD affects predominantly ethnic minorities in the United States and there are substantial disparities in wealth between white Americans and African-American and Hispanic Americans,⁶² the relevance of socioeconomic conditions to pain, functioning, and health-related quality of life is high in this population. Lower family income and greater neighborhood socioeconomic distress have been associated with greater pain-related functional disability in children with SCD pain.^{37,57} Many people with SCD report experiences of discrimination in health care encounters. The influence of stigma and perceived discrimination on health outcomes has been studied among individuals with SCD, reporting associations between higher levels of perceived disease stigma and discrimination and increased clinical and laboratory pain and health care utilization.^{7,49}

Dimension 5. Putative Neurobiological and Psychosocial Mechanisms, Risk Factors, and Protective Factors of Chronic SCD Pain

Multiple mechanisms putatively underlie the experience of pain related to SCD including acute nociceptive pain, inflammatory pain, neuropathic, and central pain processes.^{8,23} It has been postulated that multiple inputs including vaso-occlusive pain and chronic nociceptive pain as well as opioid-induced hyperalgesia from chronic opioid therapy, cause central nervous system sensitization leading to the evolution of chronic pain in SCD.^{14,70} However, whether persistent pain represents peripheral sensitization at the site(s) of tissue damage and/or central sensitization has not been well studied in humans with SCD. Similar to other chronic pain syndromes in which central pain processing alterations have been shown, individuals with SCD display several features seen in centralized pain states, such as widespread musculoskeletal pain and lower pain thresholds on quantitative sensory testing to thermal and mechanical stimuli compared with healthy control participants,^{9,12,33,34,79} altered patterns of functional connectivity of many brain regions,²⁴ a lack of response to opioid analgesia,^{3,85} and susceptibility to other pain syndromes (ie, headache).⁵⁵ Research interest has heightened in evaluating whether quantitative sensory testing may predict clinical characteristics in patients with SCD such as chronic pain (eg, Brandow and Panepinto,⁹ and Campbell et al^{11,12}).

In the absence of published diagnostic criteria, risk and protective factors for chronic SCD pain have not yet been identified. History of mental health diagnoses, somatization, and emotional factors are associated with higher admission rates for vaso-occlusive pain in individuals with SCD.^{54,74} In addition, poorer family functioning has been related to increased health care utilization in children with SCD.⁶ Similarly, in adults with patterns of frequent hospital utilization for pain management there was a 3-fold higher prevalence of psychiatric illness in family members.¹⁵ These findings may be relevant to chronic SCD pain because of their more frequent health care utilization.⁶⁶

Chronic SCD Pain Diagnostic Modifiers

Three diagnostic modifiers indicate subtypes of chronic SCD pain. The first modifier is labeled chronic SCD pain without contributory disease complications. This modifier is used if there is no evidence of contributory SCD complications on the basis of either clinical signs (eg, presence of leg ulcers) or test results (eg, imaging abnormalities). For example, a typical patient with this type of chronic SCD pain may experience daily widespread musculoskeletal pain. The second modifier is labeled chronic SCD pain with contributory disease complications. This category should be used if there is evidence of contributory SCD complications on the basis of clinical signs or test results. For example, a typical patient with this type of chronic SCD pain may have persistent localized pain at the site of a leg ulcer or bone injury. The third modifier is labeled chronic SCD pain with mixed pain types. This category in-

dicates that there is evidence of contributory SCD complications (eg, avascular necrosis) on the basis of clinical signs or test results and there is pain also occurring in unrelated pain sites (eg, arms, back, chest, or abdominal pain, headache). For example, a typical patient with this type of chronic SCD pain may have persistent pain in the hip due to avascular necrosis but also experience unrelated persistent pain in the back, chest, and arms typical of their widespread musculoskeletal pain. Research is needed to confirm and validate these modifiers and to develop specific strategies for assessment and management of chronic pain that are tailored to each subtype.

Discussion

Chronic SCD pain is a serious complication associated with increased morbidity and mortality, especially in older adolescents and adults with SCD.^{38,60,61} Currently, there is not a universally accepted classification system for chronic SCD pain. A common set of diagnostic criteria for classifying chronic SCD pain would improve clinical assessment and management of this complex condition. Indeed, recognition of chronic pain as a distinct syndrome in SCD is a relatively new concept, because of the historical focus on assessment and management of acute vaso-occlusive pain. Over the past several decades, a number of advances in medical treatment of SCD (eg, prophylaxis against infection, improved red cell transfusions, hydroxyurea therapy) have led to improved life expectancy and most patients with SCD live into at least middle adulthood. As patients age, they accumulate tissue damage as disease-related complications leading to an increasing frequency of pain, which has likely led to a change in the symptom experience of individuals with SCD over the decades. At this time, it is critical to address chronic pain and its effect on individuals with SCD.

Many studies have characterized individual complications of SCD, modeled after the SCD natural history studies initiated in the late 1970s, but few studies have tried to describe the co-occurrence of multiple SCD complications. Thus the WG believed there was insufficient evidence to currently support multiple diagnostic types of chronic SCD pain. However, their clinical experience and available literature did suggest that individuals with certain painful SCD complications of significant duration, notably leg ulcers and avascular necrosis of hips/shoulders, could occur, to varying degrees, in the absence of other more generalized SCD pain. Similarly, clinical experience and evolving psychophysical^{9,10} and neuroimaging studies²⁵ suggest the existence of widespread/multifocal pain and overlapping pain disorders in individuals with SCD consistent with central sensitization described in other chronic pain disorders.⁴⁸ In this iteration of the AAPT taxonomy, the WG chose to consider these likely subgroups as diagnostic modifiers until the results of further validation studies are available.

The WG suggested the frequency characteristic of "majority of days" for the chronic SCD pain definition corresponding to the 15 or more days per month used in the chronic migraine definition in the International

Classification of Headache Disorders. However, at this time there are not adequate data to support this cutoff in SCD or whether patterns of escalating pain frequency are associated with the subsequent development of chronic pain. An initial review of 3 years of daily pain data from a study by Dampier et al²¹ suggests that this cutoff may characterize recurrent episodic pain from chronic pain in a small group of children with SCD but requires further study in larger samples. The consideration of pain duration also was a difficult decision because few longitudinal SCD pain studies were available to inform this criterion. In the absence of appropriate data, a 6-month criterion was selected to be consistent with that used by other AAPT WGs to define chronic pain. Longer time durations may more effectively reduce misclassifying individuals with healing leg ulcers or avascular necrosis, and those with a self-limited period of acute pain exacerbations, but will require further validation in SCD. A shorter duration may be more appropriate in guiding treatment decisions, particularly in children.⁸⁴ Future versions of the AAPT taxonomy will be updated to provide more specific definitions of pain frequency and duration when validation data are collected using these diagnostic criteria in SCD.

Our WG applied a 5 axial system to identify critically important aspects of chronic pain assessment and management in SCD, which calls attention to the evidence gaps that exist in chronic SCD pain. The paucity of available research on chronic pain in SCD compared with many other chronic pain disorders significantly limited the WG's ability to apply the AAPT dimensional framework. Because much of the SCD pain literature did not make a distinction between frequent acute or persistent/chronic pain, the WG often relied on expert consensus for domain characteristics. Indeed the Expert Panel on Management of SCD⁸⁴ also relied on consensus in its guideline statement on chronic pain management and relied on general literature on chronic pain rather than evidence specifically related to chronic pain in individuals with SCD. However, the study by Sil et al,⁶⁶ which grouped children and adolescents with SCD using a pain frequency classification similar to that proposed in this report, observed only quantitative differences in several functional outcomes and psychosocial characteristics between their chronic and episodic pain groups suggesting that existing literature likely underestimates the effects of chronic SCD pain.

Considerable research will be needed to provide evidence of the reliability and validity of the criteria proposed in this report for chronic SCD pain. This iterative process has been extensively described in a companion article and would involve field testing of the criteria during clinical examinations of patients as well as empirical studies of validity.¹⁰ Although we propose 3 diagnostic modifiers to indicate subtypes of chronic SCD pain, at present there are few data that describe the frequency of each of these subtypes of pain, or whether the effect of chronic pain or prognosis differ according to chronic pain subtype. Similarly, it will be important to characterize the frequency and effects of acute recurrent vaso-occlusive pain in these

chronic pain subtypes, because this is a particularly difficult combination of pain syndromes to evaluate and treat. Research is needed to distinguish between the presence or absence of contributory disease complications as a source of chronic pain and to understand the effect of chronic SCD pain subtypes on patient functioning and quality of life across the lifespan. Because of the increase in SCD disease complications with age, it is anticipated that developmental differences will be found in the frequency of chronic pain subtypes, highlighting the importance of considering normal developmental processes that affect pain processing.⁸⁰ Such studies would also likely identify the typical age of onset for chronic pain. Moreover, it will be critical to focus research attention on developing optimal pain management strategies for individuals with different chronic SCD pain subtypes, and for management of episodic acute pain (crises) in patients with chronic SCD pain. Similarly, research is needed to identify disease management strategies that might reduce the risk of developing chronic SCD pain or improve the likelihood of its resolution.

There are several research priorities that were identified by our WG in applying an evidence-based chronic pain taxonomy to SCD pain. First, we hope this taxonomy will provide consistent criteria for conducting epidemiological studies of chronic pain prevalence and risk factors for chronic pain in individuals with SCD across the lifespan. At present, epidemiological data are drawn from a few key longitudinal diary studies, but larger sample sizes are needed to test a broad range of biopsychosocial risk factors for chronic SCD pain. Second, this taxonomy may spark interest in studies of pain mechanisms in SCD. Although it is clear that chronic SCD pain has multifactorial etiologies, at present there are limited available data on any specific mechanisms to guide treatment decisions. Studies that better characterize chronic SCD pain subtypes and phenotypes might elucidate different mechanisms for pain associated with disease complications versus for chronic SCD pain unrelated to disease complications. Third, therapeutic clinical trials in SCD would also be facilitated by use of standard inclusion/exclusion criteria for individuals with chronic SCD pain. Previous studies have focused on identifying individuals on the basis of frequency of health care utilization for acute pain, likely producing heterogeneous samples. A common set of diagnostic criteria for chronic SCD pain, such as those presented in this report, can enhance the conduct of clinical trials and lead to progress in development and testing of more effective therapies for SCD pain management.

It is important to note that the appropriate use of this classification is for evaluating chronic pain symptoms among persons with SCD. It is not appropriate to use this classification for classifying persons presenting to the Emergency Department for management of acute vaso-occlusive pain. Appropriate guidelines for management of vaso-occlusive crisis pain are available and should be followed.⁸⁴ However, when patients present for follow-up care in the outpatient setting, this classification may assist in planning the comprehensive

care for the overall management of the patient's pain characteristics.

Conclusions

This WG synthesized available literature to provide evidence for the dimensions of a disease-specific

pain taxonomy for one chronic pain syndrome labeled chronic SCD pain. Future systematic research is needed to evaluate the feasibility, reliability, and validity of the diagnostic criteria, which may lead to improved clinical assessment and management and accelerate research efforts on chronic SCD pain.

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