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REVIEW ARTICLE

Thinking beyond sickling to better understand pain in sickle cell disease

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Abstract

Painful vaso-occlusive crises (VOCs) are the hallmark of sickle cell disease (SCD); however, many patients experience frequent daily pain that does not follow the pattern of typical VOCs. This pain of variable severity, also referred as persistent pain in the SCD literature, contributes to significant morbidity and poor quality of life and often fails to respond adequately to standard SCD therapies. In this article, we briefly describe types of pain encountered in SCD with a special emphasis on persistent pain. We discuss altered pain processing as a potential contributing mechanism, which may lead to development and maintenance of persistent pain. We describe the advances in the non-SCD pain field that may help improve the understanding of SCD pain. We highlight the need for further investigation in this area because some of these patients with persistent pain may benefit from receiving adjuvant mechanism-based therapies used successfully in other non-SCD chronic pain conditions.

Key words sickle cell disease; pain; central sensitization; pain perception

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Pain in sickle cell disease

Sickle cell disease (SCD), an inherited hemoglobinopathy, is characterized by the presence of hemoglobin S (HbS), which results from the substitution of a valine for glutamic acid at the sixth amino acid of the beta-globin chain on chromosome 11 (1). Recurrent episodes of pain are the most common morbidity associated with SCD and a leading cause of visits to the emergency department (ED), hospitalizations, and healthcare costs in SCD (2). Higher rates of admission for pain are also associated with early mortality (3, 4). It is, however, now recognized that chronic pain is highly prevalent in this population and is a major source of morbidity (5). The Pain in Sickle Cell Epidemiology Study (PiSCES) showed that adults reported pain at home during about 55 percent of the 31,017 days surveyed (5). Similarly, in a study of children and adolescents with SCD, pain was reported on 2,592 days of 18,377 diary days (6). In the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), at-home analgesics were used for SCD pain on 40 percent of diary days and during 80 percent of 2-week follow-up periods, with oxycodone and codeine being used most frequently (7).

Previous reviews of pain in SCD have generally described four types of pain in the context of SCD such as acute painful vaso-occlusive crises (VOCs), neuropathic pain, chronic pain with identifiable cause, and chronic pain without obvious pathology or persistent pain (8). This review expands upon these characterizations with an emphasis on the neurobiological mechanisms that may be contributing to each of these types of pain.

Acute painful VOCs are the best characterized pain in SCD which present as sudden onset of severe pain and are often described as continuous and throbbing in nature. Acute painful VOCs often lead to a visit to emergency department or hospitalization and may be followed by other complications such as acute chest syndrome, multi-organ failure, or sudden death (9–11). The pathogenesis of VOC is

multifactorial and includes sickling of the erythrocytes caused by polymerization of sickle hemoglobin resulting in vaso-occlusion, which leads to hypoxia, ischemia, and tissue damage. Release of inflammatory mediators from injured tissue, macrophages, mast cells, and platelets activates the peripheral afferent nerves and leads to nociceptive pain (12–15). Acute painful VOCs are treated with oral or parenteral opioids and hydration and typically last for 4–7 days (8, 16). Pain-free periods between two consecutive episodes of VOCs vary but appear to shorten with increasing age (17, 18). Risk factors for frequent VOC resulting in hospitalizations include older age, higher hematocrit, lower fetal hemoglobin (HbF), and presence of alpha-thalassemia (19, 20).

Even though it is quite clear that vaso-occlusion can and do cause pain, there is tremendous interindividual variability in the pain experience across the individuals with SCD and VOC (21, 22). A subgroup of patients are at increased risk of high pain burden as shown by the Cooperative Study of Sickle Cell Disease (CSSCD) where over 30% of pain episodes were experienced by 5% of patients (19). Additionally, in some individuals, these acute episodes of pain are accompanied by clear evidence of hemolysis and other manifestations of active SCD, whereas in others there is no such evidence of active disease (8). This disparity between the degree of peripheral nociceptive input (in this case VOC) and the presence or severity of pain an individual with SCD is experiencing at any given point in time is currently not understood.

In addition to acute VOCs, other end-organ damage can also provide peripheral nociceptive input and cause pain. Etiology of such chronic pain with an identifiable cause typically includes a 'peripheral' pathology such as avascular necrosis of bone, infarcts of organs or tissues, and leg ulcers (23, 24). This pain typically improves if the peripheral pathology resolves (that is healing of an ulcer, surgical treatment of avascular necrosis). Similarly, damage to or inflammation of peripheral nerves resulting from vaso-occlusion could provide ongoing peripheral nociceptive input and contribute to pain also referred as neuropathic pain. There are limited studies characterizing neuropathic pain in SCD, which typically does not manifest itself until early or late adulthood (25–28).

Finally, another type of pain that remains a challenge for patients and physician alike is the intractable pain experienced by the patients in between the episodes of VOCs. For the purpose of this article, we refer it as chronic pain. This type of pain, which does not appear to correlate with the known markers of disease severity, is associated with high somatic symptom burden (29) and responds poorly to disease-modifying therapies such as hydroxyurea and chronic red blood cell transfusions (8, 30). This type of pain is often treated by patients at home with long- and short-acting opioids without significant relief and leads to intermittent ED visits or hospitalization for superimposed acute episodes of pain (5). Occasionally, these patients receive adjuvant therapies such as ketamine, gabapentin, physical therapy, and acupuncture with variable relief (31–33).

Recent advances in neurobiology of SCD pain

Efforts are being made to understand the pathophysiology of persistent SCD pain, which remains incompletely explained. Specifically, factors contributing to the transition of pain from acute episodic nature of VOC pain typically seen in children to persistent pain more common in adults are not known. Preliminary studies support the role of altered pain processing, a manifestation of neural plasticity, in SCD pain.

Preclinical studies

Transgenic mouse model has provided new insights into SCD pain. Mice expressing sickle hemoglobin exhibit pain characteristics similar to those observed in patients with SCD (34–36). Although some of the pain behaviors are exaggerated by hypoxia/reperfusion (37), sickle mice also appear to experience persistent pain in the absence of any traumatic, vascular, or inflammatory insult (36). These mice have increased sensitivity to nociceptive stimulus as evidenced by heat and cold hyperalgesia and mechanical hyperalgesia, which further increases with age. Furthermore, skin of sickle mice shows alteration in neurochemistry, nerve structure, and organization including fewer nerve fibers and increased expression of calcitonin-gene-related peptide (CGRP) and substance P (SP) along with up-regulation of Toll-like receptor-4 (TLR4), interleukin-6 (IL-6), STAT3, cyclo-oxygenase-2 (COX-2), and phospho-MAPK and downregulation of μ opioid receptor (MOR), changes which have been shown to be associated with peripheral and central sensitization (36, 38). In another study, Hillery *et al.*, showed that the transient receptor potential vanilloid 1 (TRPV1) channels, a mediator of thermal and mechanical hyperalgesia, are functionally activated in the primary afferents in skin–nerve preparations and in the isolated dorsal root ganglia (DRG) of BERK sickle mice. A TRPV1 channel antagonist A-425619 partially blocked the behavioral hypersensitivity to mechanical stimuli and completely reversed the nociceptor sensitization (35). Interestingly, substance P, which is known to sensitize TRPV1 channels, (39) is shown to be increased in the serum of patients with SCD (40). These findings support the hypothesis that various mechanisms including nociceptive, neuropathic, and peripheral and central sensitization contribute to SCD pain, and some of these mechanisms (neuropathic and central and peripheral sensitization) could contribute to pain in the absence of concurrent episodes of hypoxia/vaso-occlusion.

Clinical studies

Some of the findings of murine studies have been replicated in humans, supporting the altered pain processing in patients with SCD. Similar to murine model, children with SCD demonstrated lower detection threshold and increased pain sensitivity to both cold and heat compared with healthy race-matched controls (34). In another study of quantitative sensory testing (QST), children with SCD were less sensitive to heat and cold detection at the thenar eminence and more sensitive to cold pain at the forearm compared with healthy children (41). These findings suggest the potential role of altered pain sensitivity in SCD pain. Interestingly, similar to the murine model, older age was associated with decreased cold and heat pain thresholds. Epidemiologic studies have long confirmed the increasing burden of pain with age for the adults with SCD reporting pain 55% of time compared with 9% in children with SCD (6, 17, 18, 20). This phenomenon likely indicates the neuroplasticity of nervous system where functional and structural changes caused by repeated nociceptive input from the VOCs occurring overtime result in altered pain processing manifesting as increased pain experience (38).

Lessons from non-SCD pain conditions and future directions

Chronic persistent pain is a prominent symptom of many non-SCDs, ranging from disorders where there is known nociceptive input (such as, osteoarthritis, rheumatoid arthritis, neuropathic pain) to conditions where individuals have severe pain without any easily identifiable nociceptive input (e.g., fibromyalgia). In many of these painful conditions, while the disease processes are different, an underlying unifying mechanism for pain can be identified.

First, it is important to understand that there is no chronic pain condition where objective peripheral factors (e.g., the degree of joint damage, inflammation, and nerve damage) correlate well with the presence or severity of ongoing clinical pain. Perhaps, the best-known example of this is chronic low back pain, where most clinicians are aware that there is a tremendous disparity between radiographic or MRI findings and the presence or severity of pain. This is not the exception- it is the rule. The same is true of almost all of the chronic pain conditions. In cross-sectional studies, the degree of radiographic or MRI evidence of abnormalities correlates poorly with the presence or severity of pain in osteoarthritis. This is also true of rheumatoid arthritis and neuropathic pain. Most are unaware that in neuropathic pain states such as painful diabetic peripheral neuropathy, less than half of those who have objective evidence of neuropathy experience pain. In fact, many diabetics with identifiable neuropathy on nerve conduction studies have decreased sensation rather than pain (42). Thus, in individuals with SCD, we should not be surprised that even when there is an identifiable peripheral nociceptive input (e.g., active disease and likely VOC, avascular necrosis), some individuals will experience disproportionately higher or lower degree of pain. The current thinking in the pain field suggests that these large interindividual differences in pain sensitivity are largely responsible for these disparities. In both human and animal studies, within any species, there are large interindividual differences in pain sensitivity that appear to be primarily mediated by differential central nervous system processing of nociceptive input.

Genetic and environmental factors are known to affect sensitivity to pain and therefore pain experience. Temporal influence of environmental 'stressors' such as early life trauma, physical trauma, certain infections, and emotional stress has been shown to be associated with the development of either fibromyalgia or chronic fatigue syndrome (43–45). Although these 'stressors' can trigger the development of fibromyalgia and/or chronic fatigue syndrome, it occurs only in approximately 5–10% of the exposed individuals, suggesting that certain individuals are at risk for developing chronic pain state. In fact, emerging evidence suggests that individuals at risk of developing chronic pain may exhibit characteristics, which broadly represent a 'pain-prone phenotype' (46), and are portrayed in Fig. 1 (47). Although question of association vs. causality exists for some of these variables, these risk factors likely also play a role in SCD pain. Twin studies have reported the heritability estimates of pain ranging from 30% to 57%. (48, 49). Variability in the genes encoding for receptors, enzymes, or transporter channels such as GTP cyclohydroxylase, COMT, TRPV1, and KCNS1 has been implicated in non-SCD painful conditions (50–55); some of which have been examined in SCD pain (35, 56–60).

Pain associated with SCD is unique. While it dominates the clinical picture of SCD, differences and similarities exist between SCD and non-SCD pain. Unlike most non-SCD conditions associated with pain, SCD is caused by a genetic mutation, leading to the main underlying pathology of red cell sickling which affects multiple organ systems. Certain disease-modifying therapies such as hydroxyurea and chronic red blood cell transfusion can effectively reduce the disease burden, and bone marrow transplant can be curative (61–64). The symptoms of pain can start as early as 3–6 months of age, which is rare in non-SCD painful conditions; however, stress, negative mood, anxiety, and depression are associated with both SCD and non-SCD pain (65, 66). Individuals with persistent SCD pain also exhibit features such as hyperalgesia and allodynia, and many patients experience disproportionate degree of pain (19, 28, 30). We suggest that similar to some other categories of diseases with recurrent pain, individual patients with SCD may have variable pain mechanisms at play, a hypothesis that is currently being proposed in studies

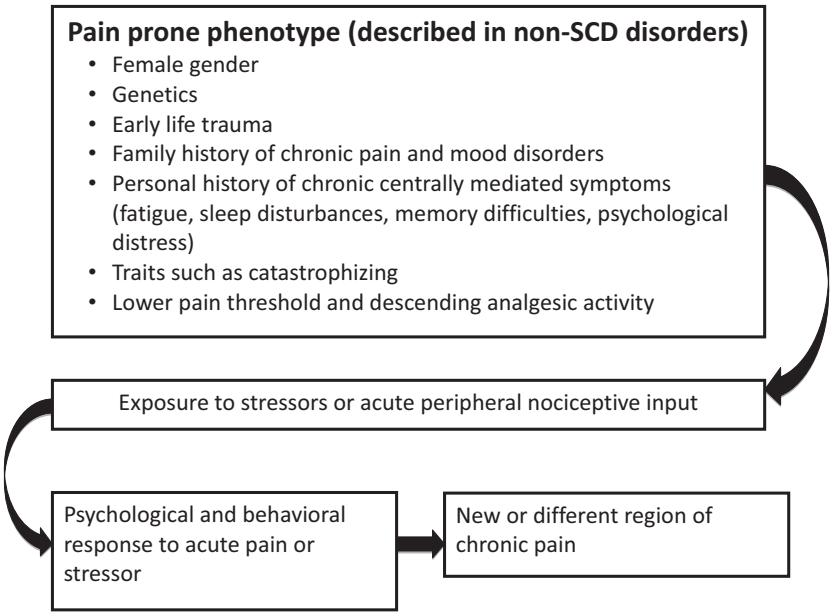

Figure 1 Factors associated with risk of developing chronic pain in non-SCD population. With permission from Philips and Clauw (47).

of SCD pain (28). SCD pain especially in adults likely reflects a mixed pain state. This term implies that individuals may have markedly different reasons for their pain. Some individuals may have pain primarily due to peripheral nociceptive input (sickling, vaso-occlusion, and release of mediators of inflammation), whereas in others, neuropathy, peripheral sensitization, and central nervous system factors (central sensitization via augmented pain processing in spinal cord and brain) may be playing an equally or even more prominent role in their pain experience. Central pain terminology was originally used to describe the pain resulting from a lesion in the CNS. Recently, the term has expanded to include the pain resulting from CNS dysfunction or mechanisms, which might contribute to the development or maintenance of pain including important contributions from psychosocial aspects of pain perception (67). The term central sensitization in the context of chronic pain indicates increased sensitivity of CNS to peripheral afferent pain signals, which has been validated by newer tools such as functional neuroimaging by providing objective evidence of altered pain processing in many chronic pain conditions (68, 69).

For several decades now, pain researchers have been suggesting that it might be more appropriate to treat chronic pain based on the underlying mechanism of pain in addition to the disease that leads to the pain (70, 71). Using this type of schema, pain can be mechanistically classified as peripheral/nociceptive, peripheral neuropathic/sensitization, and central neuropathic/sensitization or centralized pain (Table 1) (72). A point of emphasis is that any of these mechanisms may be operative simultaneously in the same patient. To treat the patient adequately, all potential mechanisms must be identified in a given individual because the treatments

Table 1 Mechanistic characterization of pain[1]

	Peripheral/nociceptive	Peripheral neuropathic/sensitization	Central neuropathic/sensitization
Underlying mechanism	Inflammation or mechanical damage of tissues	Damage or dysfunction of peripheral nerves	Altered central pain processing
Pain characteristics	Throbbing, sharp, pounding, dull Local	Burning, heavy sensation, or numbness along the path of the affected nerve. Allodynia and hyperalgesia	Hyperalgesia/allodynia Diffuse pain
Response to therapy	NSAID, opioid responsive	Responds to both peripheral and centrally acting pharmacological therapies, gabapentinoids	Responsive to neuroactive compounds altering levels of neurotransmitters of pain
Classic examples	Osteoarthritis Rheumatoid arthritis ? SCD acute VOC	Diabetic neuropathic pain Postherpetic neuralgia SCD-related peripheral neuropathies ? SCD persistent pain	Fibromyalgia Irritable bowel syndrome TMJD Tension headache ? SCD chronic pain

[1]Adapted from Phillips and Clauw with permission (72).

that may work for these different types of pain are much different (68, 70, 71). It is possible that some individuals with SCD have evidence of centralization of pain and may benefit from adjuvant centrally acting treatments such as selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), gabapentinoids, or tricyclics (73–75), whereas other individuals may have peripheral contributions to their pain that may respond well to therapies directed at lowering the polymerization of sickle hemoglobin and vaso-occlusion. Recently, a phase I study of FDA-approved drug for treatment of psychotic conditions, trifluoperazine, a known inhibitor of CaMKIIα implicated in neuropathic pain has shown promising results in SCD (76).

In conclusion, the etiology of chronic pain in SCD is likely multifactorial. We propose that similar to non-SCD chronic pain, these patients may have additional mechanisms of pain at play and may benefit from adjuvant-mechanism-based therapy. However, as we adopt and borrow these concepts from non-SCD pain research, it is crucial to validate their applicability to SCD, which has an obvious etiology for pain, caused by the presence of sickle gene and sickle hemoglobin.

Conflict of interest and sources of funding

None.

References

1. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med* 1997;**337**:762–9.
2. Steiner CA, Miller JL. Sickle Cell Disease Patients in U.S. Hospitals, 2004: Statistical Brief #21. 2006.
3. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;**330**:1639–44.
4. Darbari DS, Wang Z, Kwak M, *et al.* Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. *PLoS ONE* 2013;**8**:e79923.
5. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med* 2008;**148**:94–101.
6. Dampier C, Ely E, Brodecki D, O'Neal P. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. *J Pediatr Hematol Oncol* 2002;**24**:643–7.
7. Ballas SK, Bauserman RL, McCarthy WF, Castro OL, Smith WR, Waclawiw MA. Hydroxyurea and acute painful crises in sickle cell anemia: effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home. *J Pain Symptom Manage* 2010;**40**:870–82.
8. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood* 2012;**120**:3647–56.
9. Vichinsky EP, Neumayr LD, Earles AN, *et al.* Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;**342**:1855–65.
10. Hassell KL, Eckman JR, Lane PA. Acute multiorgan failure syndrome: a potentially catastrophic complication of severe sickle cell pain episodes. *Am J Med* 1994;**96**:155–62.
11. Manci EA, Culberson DE, Yang YM, Gardner TM, Powell R, Haynes J Jr, Shah AK, Mankad VN. Causes of death in sickle cell disease: an autopsy study. *Br J Haematol* 2003;**123**:359–65.
12. Francis RB Jr, Johnson CS. Vascular occlusion in sickle cell disease: current concepts and unanswered questions. *Blood* 1991;**77**:1405–14.
13. Kaul DK, Hebbel RP. Hypoxia/reoxygenation causes inflammatory response in transgenic sickle mice but not in normal mice. *J Clin Investig* 2000;**106**:411–20.
14. Platt OS. Sickle cell anemia as an inflammatory disease. *J Clin Invest* 2000;**106**:337–8.
15. Vincent L, Vang D, Nguyen J, Gupta M, Luk K, Ericson ME, Simone DA, Gupta K. Mast cell activation contributes to sickle cell pathobiology and pain in mice. *Blood* 2013;**122**:1853–62.
16. Ballas SK, Lieff S, Benjamin LJ, *et al.* Definitions of the phenotypic manifestations of sickle cell disease. *Am J Hematol* 2010;**85**:6–13.
17. McClish DK, Smith WR, Dahman BA, Levenson JL, Roberts JD, Penberthy LT, Aisiku IP, Roseff SD, Bovbjerg VE. Pain site frequency and location in sickle cell disease: the PiSCES project. *Pain* 2009;**145**:246–51.
18. Dampier C, Ely B, Brodecki D, O'Neal P. Characteristics of pain managed at home in children and adolescents with sickle cell disease by using diary self-reports. *J Pain* 2002;**3**:461–70.
19. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med* 1991;**325**:11–6.
20. Darbari DS, Onyekwere O, Nouraie M, *et al.* Markers of severe vaso-occlusive painful episode frequency in children and adolescents with sickle cell anemia. *J Pediatr* 2012;**160**:286–90.
21. Diggs LW. The crisis in sickle cell anemia; hematologic studies. *Am J Clin Pathol* 1956;**26**:1109–18.
22. Ballas SK. *Sicle Cell Pain*. Seattle WA: IASP Press, 1998.
23. Minniti CP, Delaney KM, Gorbach AM, *et al.* Vasculopathy, inflammation, and blood flow in leg ulcers of patients with sickle cell anemia. *Am J Hematol* 2014;**89**:1–6.
24. Ballas SK, Kesen MR, Goldberg MF, *et al.* Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. *ScientificWorldJournal* 2012;**2012**:949535.
25. Wilkie DJ, Molokie R, Boyd-Seal D, Suarez ML, Kim YO, Zong S, Wittert H, Zhao Z, Sauntharajah Y, Wang ZJ. Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. *J Natl Med Assoc* 2010;**102**:18–27.

26. Smith WR, Scherer M. Sickle-cell pain: advances in epidemiology and etiology. *Hematology Am Soc Hematol Educ Program* 2010;**2010**:409–15.
27. Ballas SK, Darbari DS. Neuropathy, neuropathic pain, and sickle cell disease. *Am J Hematol* 2013;**88**:927–9.
28. Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. *Pediatr Blood Cancer* 2014;**61**:512–7.
29. Sogutlu A, Levenson JL, McClish DK, Rosef SD, Smith WR. Somatic symptom burden in adults with sickle cell disease predicts pain, depression, anxiety, health care utilization, and quality of life: the PiSCES project. *Psychosomatics* 2011;**52**:272–9.
30. Molokie RE, Wang ZJ, Wilkie DJ. Presence of neuropathic pain as an underlying mechanism for pain associated with cold weather in patients with sickle cell disease. *Med Hypotheses* 2011;**77**:491–3.
31. Jennings CA, Bobb BT, Noreika DM, Coyne PJ. Oral ketamine for sickle cell crisis pain refractory to opioids. *J Pain Palliat Care Pharmacother* 2013;**27**:150–4.
32. Lu K, Cheng MJ, Ge X, Berger A, Xu D, Kato GJ, Minniti CP. 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* 2013. [Epub ahead of print].
33. 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**:334–40.
34. Brandow AM, Stucky CL, Hillery CA, Hoffmann RG, Panepinto JA. Patients with sickle cell disease have increased sensitivity to cold and heat. *Am J Hematol* 2013;**88**:37–43.
35. Hillery CA, Kerstein PC, Vilceanu D, Barabas ME, Retherford D, Brandow AM, Wandersee NJ, Stucky CL. Transient receptor potential vanilloid 1 mediates pain in mice with severe sickle cell disease. *Blood* 2011;**118**:3376–83.
36. Kohli DR, Li Y, Khasabov SG, *et al.* Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids. *Blood* 2010;**116**:456–65.
37. Cain DM, Vang D, Simone DA, Hebbel RP, Gupta K. Mouse models for studying pain in sickle disease: effects of strain, age, and acuteness. *Br J Haematol* 2012;**156**:535–44.
38. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;**10**:895–926.
39. Zhang H, Cang CL, Kawasaki Y, Liang LL, Zhang YQ, Ji RR, Zhao ZQ. Neurokinin-1 receptor enhances TRPV1 activity in primary sensory neurons via PKCepsilon: a novel pathway for heat hyperalgesia. *J Neurosci* 2007;**27**:12067–77.
40. Michaels LA, Ohene-Frempong K, Zhao H, Douglas SD. Serum levels of substance P are elevated in patients with sickle cell disease and increase further during vaso-occlusive crisis. *Blood* 1998;**92**:3148–51.
41. O'Leary JD, Crawford MW, Odame I, Shorten GD, McGrath PA. Thermal pain and sensory processing in children with sickle cell disease. *Clin J Pain* 2014;**30**:244–50.
42. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract* 2000;**47**:123–8.
43. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury [see comments]. *Arthritis Rheum* 1997;**40**:446–52.
44. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *NeuroImmunoModulation* 1997;**4**:134–53.
45. Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am* 2009;**35**:233–51.
46. Diatchenko L, Fillingim RB, Smith SB, Maixner W. The phenotypic and genetic signatures of common musculoskeletal pain conditions. *Nat Rev Rheumatol* 2013;**9**:340–50.
47. Phillips K, Clauw DJ. Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis Rheum* 2013;**65**:291–302.
48. MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. *Arthritis Rheum* 2004;**51**:160–7.
49. Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Heritability of low back pain and the role of disc degeneration. *Pain* 2007;**131**:272–80.
50. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003;**299**:1240–3.
51. van Meurs JB, Uitterlinden AG, Stolk L, Kerkhof HJ, Hofman A, Pols HA, Bierma-Zeinstra SM. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. *Arthritis Rheum* 2009;**60**:628–9.
52. Costigan M, Belfer I, Griffin RS, *et al.* Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. *Brain* 2010;**133**:2519–27.
53. Tegeder I, Costigan M, Griffin RS, *et al.* GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* 2006;**12**:1269–77.
54. Amaya F, Wang H, Costigan M, *et al.* The voltage-gated sodium channel Na(v)1.9 is an effector of peripheral inflammatory pain hypersensitivity. *J Neurosci* 2006;**26**:12852–60.
55. Hendry L, Lombard Z, Wadley A, Kamerman P. KCNS1, but not GCH1, is associated with pain intensity in a black southern African population with HIV-associated sensory neuropathy: a genetic association study. *J Acquir Immune Defic Syndr* 2013;**63**:27–30.
56. Lettre G, Sankaran VG, Bezerra MA, *et al.* DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci

associate with fetal hemoglobin levels and pain crises in sickle cell disease. *Proc Natl Acad Sci U S A* 2008;**105**:11869–74.
57. Mahdi N, Abu-Hijleh TM, Abu-Hijleh FM, Sater MS, Al-Ola K, Almawi WY. Protein Z polymorphisms associated with vaso-occlusive crisis in young sickle cell disease patients. *Ann Hematol* 2012;**91**:1215–20.
58. Al-Habboubi HH, Mahdi N, Abu-Hijleh TM, Abu-Hijleh FM, Sater MS, Almawi WY. The relation of vascular endothelial growth factor (VEGF) gene polymorphisms on VEGF levels and the risk of vasoocclusive crisis in sickle cell disease. *Eur J Haematol* 2012;**89**:403–9.
59. Sheehan VA, Luo Z, Flanagan JM, Howard TA, Thompson BW, Wang WC, Kutlar A, Ware RE. Genetic modifiers of sickle cell anemia in the BABY HUG cohort: influence on laboratory and clinical phenotypes. *Am J Hematol* 2013;**88**:571–6.
60. Belfer I, Youngblood V, Darbari DS, *et al.* A GCH1 haplotype confers sex specific susceptibility to pain crises and altered endothelial function in adults with sickle cell anemia. *Am J Hematol* 2014;**89**:187–93.
61. Wang WC, Ware RE, Miller ST, *et al.* Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011;**377**:1663–72.
62. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;**332**:1317–22.
63. Hsieh MM, Kang EM, Fitzhugh CD, Link MB, Bolan CD, Kurlander R, Childs RW, Rodgers GP, Powell JD, Tisdale JF. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. *N Engl J Med* 2009;**361**:2309–17.
64. Miller ST, Wright E, Abboud M, Berman B, Files B, Scher CD, Styles L, Adams RJ. 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**:785–9.
65. Gil KM, Carson JW, Porter LS, Ready J, Valrie C, Redding-Lallinger R, Daeschner C. Daily stress and mood and their association with pain, health-care use, and school activity in adolescents with sickle cell disease. *J Pediatr Psychol* 2003;**28**:363–73.
66. Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, de ACV, Penberthy LT, Aisiku IP, Roberts JD, Roseff SD, Smith WR. Depression and anxiety in adults with sickle cell disease: the PiSCES project. *Psychosom Med* 2008;**70**:192–6.
67. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain* 2009;**10**:777–91.
68. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;**152**(3 Suppl):S2–15.
69. Jensen KB, Berna C, Loggia ML, Wasan AD, Edwards RR, Gollub RL. The use of functional neuroimaging to evaluate psychological and other non-pharmacological treatments for clinical pain. *Neurosci Lett* 2012;**520**:156–64.
70. Max MB. Is mechanism-based pain treatment attainable? Clinical trial issues *J Pain* 2000;**1**(3 Suppl):2–9.
71. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004;**140**:441–51.
72. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states–maybe it is all in their head. *Best Pract Res Clin Rheumatol* 2011;**25**:141–54.
73. Fishbain DA, Detke MJ, Wernicke J, Chappell AS, Kajdasz DK. The relationship between antidepressant and analgesic responses: findings from six placebo-controlled trials assessing the efficacy of duloxetine in patients with major depressive disorder. *Curr Med Res Opin* 2008;**24**:3105–15.
74. Tzellos TG, Papazisis G, Amaniti E, Kouvelas D. Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol* 2008;**64**:851–8.
75. Bohren Y, Tessier LH, Megat S, *et al.* Antidepressants suppress neuropathic pain by a peripheral beta2-adrenoceptor mediated anti-TNFalpha mechanism. *Neurobiol Dis* 2013;**60**:39–50.
76. Molokie RE, Wilkie DJ, Wittert H, Suarez ML, Yao Y, Zhao Z, He Y, Wang ZJ. Mechanism-driven phase I translational study of trifluoperazine in adults with sickle cell disease. *Eur J Pharmacol* 2014;**723**:419–24.

