Pain Management for the Sickle Cell Patient

Thomas Zouki, Armen Haroutunian and Tennison Malcolm

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79495

Abstract

Sickle cell disease (SCD) is a condition very common in the United States of America and its most common presenting symptom is pain related to vaso-occlusive events (VOE). The cost associated with healthcare for the sickle cell population exceeds 1 billion $USD yearly, and the majority of this cost is associated with admission related to vaso-occlusive events. With the increase longevity of patients with SCD, due to new therapies and vaccination against common infection related to SCD, the prevalence of older individuals experiencing VOE will likely increase. The psychological impact inflicted on patients with SCD can further complicate adequate care of patients experiencing acute or chronic pain and the latter must be taken into consideration when planning an optimal treatment regimen. This chapter reviews the short- and long-term management options of pain related to VOE, their limitations as well proposed regimen that could pave the way for the future of pain management of SCD.

Keywords: sickle cell anemia, sickle cell pain, sickle cell crises, sickle cell disease, vaso-occlusive event, sickle cell pain management, pain management

1. Introduction

Sickle cell disease (SCD) is a term used for a collective group of autosomal recessive disorders involving the abnormal structure of hemoglobin where both alleles of the beta chain of hemoglobin gene are affected, and at least one of them being affected by a sickle cell mutation. This mutation results from a single nucleotide change (GAT → GTT) in the sixth codon of the first exon of the beta-globin gene, resulting in the substitution of glutamic acid to valine (HbS) [1]. When an individual inherits two sickle cell genes (one from each parent, Hb S/S), he or she...
is affected with sickle cell anemia. The Hb S/S mutation is the most common form of SCD, it accounts for 60–70% of SCD in the United States. Other forms result from a coinheritance of an HbS allele with another abnormal β-globin chain, HbC (Hb S/C) and from a β-thalassemia (Hb S/β+, Hb S/β0) being the most common among others. The mutation results in a beta chain of the hemoglobin molecule that is more hydrophobic compared to its normal counterpart (HbB) and is prone to polymerization during episodes of lower oxygen tension, hypothermia or many other stressors. A deoxygenated hemoglobin B (HbB) of patients with SCD will aggregate along its molecular axis leading to distortion of the cell membrane and giving it a sickle shape appearance. A hallmark of sickle cell disease is intermittent vaso-occlusive events (VOE) and chronic hemolytic anemia. VOE in acute and chronic pain as well as organ damage most notably to the bones, spleen, liver, brain, lungs, kidneys and joints [2].

SCD is a disease that is mostly present in persons of African, Mediterranean, Middle Eastern and Indian ancestry but has been found in individuals of any ethnic background. The prevalence of sickle cell trait, among African Americans in the United States, is 10%, or 3.5 million people, leading to the incidence of SCD among this ethnic group of approximately 1 in 365 live births. More than 100,000 individuals in the United States are estimated to suffer from SCD. In the United Kingdom, the prevalence is about 12,500 people. Globally, it is estimated that about 5–7% of the world’s population are carriers of the mutant hemoglobin gene [3, 4], most of which residing on the African continent. As a matter of fact, about 15 million Africans are affected by SCD, more than all other continents combined. And about 200–300,000 affected births per year occur on the African continent [4, 5], accounting for more than 75% of the SCD newborns worldwide. Globally, SCD is one the four most common autosomal recessive diseases along with cystic fibrosis, thalassemia and Tay-Sachs.

Although in some areas of the world, such as Western African countries, where new treatment modalities are not as widely accessible, SCD accounts for as many as 16% of deaths in children under 5 years old, the death rate has remarkably been reduced in the United States in recent times. In fact, many children did not live to adulthood about half a century ago. With the emergence of hydroxyurea, new born screening, newer and better antibiotics as well as the introduction of the pneumococcal vaccine, the lifespan for sickle cell individuals in the United States has increased substantially to 48 years old for female and 42 years old for male. As a matter of fact, the median survival age of patients with SCD living between 1910 and 1950 was below 20 years of age [6]. By 1980, 50% of children survived beyond 20 years of age; and by 2009, 85% of SCD affect patients did. In England, the trend for hospital admissions related to SCD has been on the rise; from 2001/2002 to 2009/2010, admissions with a diagnosis of SCD have risen by more than 50%.

The management of SCD is complex and multidisciplinary. Supportive management includes regular follow-ups with the healthcare providers, adequate diet and sleep. Symptomatic management targets symptoms of the disease and include blood transfusions, pain management, antibiotics for infections among many other possible treatments. Preventive managements include vaccinations, avoidance of stressors that triggers crisis, hydroxyurea treatment, transfusion, etc. Abortive therapy is the attempt at preventing painful crisis from getting worse and leading to other complications. They include nitrous oxide and anti-adhesion factors. The ultimate goal is curative therapy, which can arise from stem cell transplantation, and gene therapy in the future. This chapter focuses solely on the pain management of patients with SCD and is divided into acute pain, chronic pain and neuropathic pain.
2. Pathogenesis of sickle cell pain

Sickle cell related pain is classified into three categories: acute pain, chronic pain and neuropathic pain [7]. Acute pain is, by far, the most commonly encountered type of pain by healthcare providers and is the precursor of chronic and neuropathic pain. The pathophysiology of sickle cell pain is still not completely understood but is thought to be initiated by stress/deoxygenation leading to the polymerization of sickle Hb in the red blood cells (RBC) inside the micro and macro-vasculature. This causes the RBC to lose its deformability and adhere to the vascular endothelium that in turn gets activated. The latter participates in the recruitment of white blood cells (WBC), which further accentuates the existing vascular occlusion and facilitates tissue ischemia and damage. The activation of endothelial cells along with the tissue damage provokes the release of inflammatory mediators (including arachidonic acid, histamines, bradykinin, H+, K+, cytokines, serotonin, substance P, leukotrienes among others) [8, 9]. The combination of tissue damage and the resulting secondary inflammatory process generated is thought to be the cornerstone of the pain perceived during VOE. They convert chemical and mechanical energy into electrochemical impulse. The release of interleukin-1 activates the cyclo-oxygenase (COX) system that in turns converts arachidonic acid into prostaglandins E2 and I2. This inflammatory soup created interacts to permit and facilitate the transduction and transmission of the painful stimuli from the periphery the central nervous system via the nerve endings, spinal cord and the thalamus. Some of the mediators (Substance P and bradykinin) also cause vasodilatation and extravasation of fluid leading to focal edema and tenderness in the affected areas.

The peripheral nociceptors involved in the painful cascade send their signals via fast acting A-delta and slow acting C fibers to the dorsal horn of the spinal cord by means of the dorsal root ganglion. From the dorsal horn of the spinal cord, the pain signals travel contralaterally through the spinothalamic tract to the thalamus that in turn has multiple interconnections with other systems such as the limbic system (mediator of memory and emotion), the reward system (mediator of pleasure and addiction) and the glia. The signals are then either facilitated or suppressed at the level of the spinal cord by different modulators. The N-methyl-D-aspartate (NMDA) receptor is probably the most important receptor involved in the facilitation of pain transmission. Other important modulators include endogenous endorphins, serotonin and norepinephrine. With knowledge of the implicated factors involved in sickle cell pain, better management can be made targeting the involved transmitters, receptors and modulators.

3. Acute pain: the vaso-occlusive event

The vaso-occlusive event (VOE) is the most common cause of morbidity in the patients with SCD [10]. VOE also account for the most common cause of hospital admissions and missed school days. Some data report that up to 95% of hospital admissions related to SCD are for acute painful crises [11, 12]. Multicellular aggregates leading to blood flow obstruction in small blood vessels, depriving downstream tissues of oxygen and nutrient constitute the painful pathway of VOE, which was described earlier in this chapter. Although VOE-related pain can affect any part of the body and often cause generalized pain, it more commonly presents as pain in the extremities in the pediatric population, as opposed to being more commonly
seen as headache, chest pain, abdominal and back pain in older individuals [13]. The average duration of an acute pain crisis, based on hospital length of stay, is about 7 days [7]. Fever and leukocytosis typically accompany the patient’s presentation and the extent of WBC tends to correlate with the degree of pain [14, 15]. Also, the higher the level of Hb and hematocrit is, the more likely it is that a VOE will occur [9]. Even if leukocytosis associated with VOE does not necessarily signify an infectious process, careful evaluation should be undertaken, as these individuals are highly susceptible to pathogens. A careful and thorough history and physical examination should be undertaken. Inquiring about the onset, location, radiation, quality, relieving and aggravating factors associated with the current painful episode, any differences between the current episode and previous episodes, the presence of fever, transfusion history, medications, baseline hemoglobin level, and a thorough physical exam can assist in making a more definite diagnosis. Any atypical presentation should prompt further investigation (Table 1). The triggers of VOE can be physical, psychological, physiological and environmental among many. At any age group, a painful crisis typically begins with sudden onset of pain.

Although most individuals with SCD presenting to the healthcare professional with VOE will exhibit different types complains as far as onset, location, quality and intensity of their pain, the painful crisis will typical last between 7 and 10 days and can be described as possessing four different phases: A prodromal phase, initial phase, established phase and resolving phase [16–18]. A prodromal phase lasts 1–2 days and consists of aches, numbness or paresthesia in the area that will subsequently become painful. Physical signs of the prodromal phase include loss of usual appearance of the eyes (loss of luster or yellowing of the eyes). Laboratory values are significant for a decrease in erythrocyte deformability and increase density of erythrocytes. The second phase, initial phase, also lasting 1–2 days, is characterized by an increase in pain level and laboratory findings such as decreased RBC deformability, increase in the number of dense cells, red cell distribution width (RDW), reticulocytosis, leukocytosis, and relative

1. Detailed history:
   - Pain: onset, location, radiation, quality, frequency, progressiveness, alleviating and aggravating factors, home medications.
   - Presence of fever
   - Transfusion history
   - Baseline hemoglobin
   - Associated factors (Cough and respiratory symptoms, GI symptoms, neurological changes)

2. Thorough physical exam
   - Body temperature
   - Areas of tenderness
   - Cardiac, pulmonary, skin, CNS, abdominal

3. Laboratory results (BMP, CBC)

4. Radiologic imaging based on history and physical (i.e., Abdominal CT for abnormal abdominal pain, Head CT if any CNS manifestation present)

5. Initiate pain management algorithm (Figure 1) after serious complications rules out (stroke, acute chest syndrome, splenic sequestration, pneumococcal sepsis, priapism)

Table 1. Primary investigation upon initial presentation of a SCD patient in pain.
thrombocytopenia. The third phase, the established phase, is when the pain level is at its peak. The patient will show signs of frustration, depression, will tend to complain about hospital staff due to lack of appropriate treatment. Physical exam will show an elevated temperature, signs of inflammation, joint effusions. Laboratory signs will consist of elevated WBC, decreased Hb, and elevated reticulocyte count, elevated LDH, CPK and CRP. This phase is the longest for an average of about 4–5 days. The fourth and final phase, lasting 3 days on average, is the resolving phase; patients start showing signs of decreasing pain, RBC deformability increases, as well as fibrinogen, orosomucoid, ESR, platelets and plasma viscosity. The blood level of sickled RBC is decreased during the final phase. The increase in plasma viscosity leads to a hypercoagulable state that becomes a culprit for recurrence of another painful crisis. In fact, about 16% of hospital admissions because of VOE get readmitted with recurrence within 1 week of discharge [11, 19]. The reasons for readmissions include, but not limited to, withdrawal syndrome, premature discharge, inadequate pain management during hospital admission, development of tolerance to opioid medications, opioid-induced hyperalgesia (OIH). Analysis of children admitted to hospitals with VOE show that patients typically show a blunted response to pain relief after the fourth to sixth day of admission [20]. The reason for this phenomenon is unknown but could be related to OIH, tolerance or provider inexperience with prolonged VOE pain. This subset of patients is more likely to return to the hospital and get readmitted. Special attention should be paid to readmitted patient since these tend to have a higher morbidity and mortality rate. Also, care should be taken not to under treat patients in the resolving phase of the VOE; Even if the pain seems to subside during this phase, it is important to continue aggressive pain management, provide patients with appropriate discharge instructions to avoid overdose or withdrawal after discharge, arrange for appropriate follow-up.

This table points out important factors to consider when doing a primary investigation of a SCD patient presenting to the ED in pain. It is important to perform a full assessment of the patient to rule out any serious adverse events that are commonly associated with SCD.

3.1. Treatment of acute sickle cell pain

The first time SCD was recognized as its own disease was in 1910 when a medical resident observed the sickle appearing cell under a microscope [21]. Since then, many more discoveries about the disease were made, and its treatment still remains a dynamic process with changes constantly occurring. The therapeutic research initially consisted of finding ways to prevent the blockage of small blood vessels by the sickles shape RBC [22]. It was not until the 1960s that pain was recognized as a major symptom in SCD. Among the first pharmacological approaches used to treat it figured papaverine and acetaminophen [23]. It was not until later that opioid medications were used for the treatment of SCD and now represents the cornerstone of treatment for acute painful crisis. Appropriate treatment of VOE crisis is crucial since the consequences associated with the latter are many. Those involve acute chest syndrome in about 50% of VOE-related hospitalization, acute multi-organ failure and sudden death [24–26]. Aborting the acute painful episode at the prodromal phase could potentially prevent or minimize tissue damage [16]. A wide range of treatment modalities exists for the treatment of acute sickle cell pain. Nonpharmacological approaches such as acupuncture, heat, ice, relaxation techniques and hypnosis but are not covered in detail in this chapter [9, 27–30]. Pharmacological approaches for the treatment of VOE around the globe consist predominantly of opioid...
analgesic including full agonists, partial agonists, mixed agonists-antagonists, antagonists but also include opioid adjuvants as well as nonopioid analgesics such NSAIDs, acetaminophen and other adjuvants [9]. As previously mentioned, VOE is the most common presentation (up to 90%) of patients with SCD to the healthcare facilities (i.e., Emergency Department). The first step in management focuses on immediate pain control with fluids and analgesics as evidence exists demonstrating that rapid and efficient control of acute pain related to VOE reduces pain scores, length of hospital stay, improve patient satisfaction [28, 31], reduce hospitalization in patients with SCD and also a decrease in the development of chronic pain syndromes, which is commonly seen in the sickle cell population [9, 32].

However, managing the pain could be more difficult than anticipated by the healthcare provider, as the SCD patient’s pain management differs from that of the rest of the population. Indeed, the patient with sickle cell disease tends to be more tolerant to opioid medications then the rest of the population due to chronic administration, VOE pain can appear out of proportion for most providers and necessitates higher doses of narcotics which most emergency department providers are not accustomed to administer. This underlines the reason why most patients with sickle cell disease report that their pain is undertreated in the emergency department and that the providers lack understanding and compassion [9, 33–38]. Additionally, VOE-related pain more exaggerated than expected, every patient possesses his own unique sensation, perception and expression of pain.

Indicators of adequate VOE management consist, but not limited to, admission to the hospital (indicates poor pain control in the ED), readmission to the hospital (indicator that pain was not well controlled during hospital stay), length of stay (indicator of effective pain management during hospital stay), pain intensity felt during ED visit or hospitalization (different pain measurement assessment available), patient and parents satisfaction, increase or decrease in VOE/SCD-related complications (Table 2).

The indicators of an effective treatment of SCD patients during their visit to the ED or admission to the hospital are shown here. Signs of ineffective treatment are admission from the ED to the hospital, readmission to the hospital after discharge, increased length of stay in the ED or the hospital, elevated pain assessment score, poor patient and/or parent satisfaction.

Facilities that have taken into account these indicators of effective VOE pain management have demonstrated benefit in rapid treatment of patients presenting to their healthcare facility with VOE with an individualized plan for each patient. An individualized plan results in decreased hospital admissions, readmissions, length of ED and hospitalization, substantial decrease in pain scores, increased patient and parent satisfaction. Although no single plan or approach is perfect for all patients, there are different algorithms that are available to the healthcare provider that serve as helpful guide for the patient presenting with VOE. Using an algorithm has shown to be simple, cost-effective and beneficial for the patient’s generalized well-being. Institutions that commonly encounter patients with VOE are encouraged to either follow an existing effective algorithm or create their own. Every patient presenting to the healthcare provider with VOE-related pain would require his or her own individualized treatment plan [39]. Our preferred algorithm is inspired by the American Pain Society and is detailed in the following paragraph.
This figure outlines our guidelines for the recommendation of the treatment of VOE in the ED. Alternatively, institution that do not typically encounter individuals with SCD and that do not have an algorithm in place for the management of a patient that presents to their healthcare facility for the first time should involve starting with the lowest dose for the shortest duration possible in order to control the symptoms if the pain is mild to moderate and the patient has not been opioid naïve [39]. If the pain is moderate to severe and the patient has previously attempted an opioid medication without relief, a higher dose of opioid is preferred. From that baseline, the physician should titrate the dose, and duration of the analgesic medications upwards until adequate pain relief is achieved. On the other hand, as discussed earlier, the patient who presents for a subsequent visit to the same healthcare facility should initially be restarted on the same analgesic regimen with which adequate pain relief was obtained in the previous visits for VOE crises.

Figure 1. Management of SCD patient presenting to the ED with VOE.
Whenever initiating opioid analgesia, it is mandatory to monitor for respiratory and sedation status. Useful questionnaires such as the Richmond Agitation Sedation Scale (RASS), the visual analogue scale (VAS) exist for sedation and pain assessment respectively. Respiratory status is typically monitored by pulse oximetry and visual assessment although some institution advocate for continuous end-tidal carbon dioxide monitoring (EtCO₂), especially when using high doses of opioids.

The preferred and recommended primary pharmacological method to treat the VOE crises is the opioid analgesic route and the commonly used medications include codeine, morphine, hydromorphone, fentanyl, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxymorphone, oxycodone, methadone and diamorphine [9].

3.2. Opioid medications

The first opiate used for VOE in the ED was meperidine in the 1960s. At home, short-acting oxycodone with acetaminophen was the most often used home medication. Morphine sulfate then got FDA approval in the 1980s and became the opiate of choice for the management of VOE in the 1990s. Not only did morphine show improvement in pain management and decreased hospital admissions related to VOE, it also did not possess the feared seizure side effect related to the meperidine metabolites, Normeperidine. These metabolites reduce the seizure threshold and also accumulate in patient with renal insufficiency, a complication commonly seen in patients with SCD [40–42]. In today’s world though, as mentioned earlier, many different types of opioid are used effectively for the treatment of VOE-related pain but in the United States, intravenous hydromorphone is the drug most commonly used in the hospital setting and oral oxycodone as home prescription medications [43]. As a comparison, in the United Kingdom, intravenous morphine, diamorphine and oral oxycodone are the most commonly used pain medications for VOE pain.

Opioid agonists produce their effect by binding into μ receptors. The potency of a particular opioid is dependent on the binding affinity or strength with which that drug binds to its receptors and there is a great amount of variability of potency between different opiates. For example, hydromorphone is 5–7 as potent as morphine while sufentanyl is 500–1000 as potent as morphine. When an opiate binds to its receptors, it initiates a cascade of biochemical events that starts with activation of G-proteins, inhibition of adenylate cyclase activity and extrusion of K⁺ that result in hyperpolarisation of cell membranes, which delays or prevents the transmission of

---

Table 2. Indicators of effective/ineffective VOE treatment.

| Indicator                        |
|----------------------------------|
| 1. Admission to the hospital     |
| 2. Readmission to the hospital   |
| 3. Length of stay in the ED or hospital |
| 4. Patient pain assessment (i.e., VAS, Baker-Wong faces scale) |
| 5. Patient satisfaction          |
| 6. Parent satisfaction           |

---

Pain Management in Special Circumstances

22
painful stimuli. Additionally, there exists a multitude of different receptors that each mediates the desired analgesic differently. Thus, the response to opioids depends not only on the type of opioid used, but also on the number and activity of the opioid receptors that a certain patient has. An opioid that binds a low number of receptors and has poor affinity, for example, is unlikely to produce effective analgesia in certain patients even if the dose is high. On the other hand, an opioid binding to an elevated number of receptors and with moderate or high binding affinity would provide effective analgesia even if used in small doses. This is part of the reason, among many others, why there is an immense variability to the pain response in patients with SCD. A dose considered an under treatment for a particular patient could overdose another patient.

3.3. Opioids adverse events

Unfortunately, opioids are not without side effects. The long list of mild to moderate adverse effects includes pruritus, nausea, vomiting, constipation, urinary retention, seizures, hives and the notorious respiratory depression. As mentioned earlier, seizures are mostly associated with meperidine. Other opioids have also possessed a potential for albeit a lot smaller and thought to be derived from the neuroexcitation related to metabolite of the opiate. Opioid-induced pruritus is one of the most prevalent complications with the use of opioids and is typically well controlled by either hydroxyzine, diphenhydramine, low dose naloxone and, now recognized as the most effective treatment, nalbuphine. The more serious complications, some of which are very popular topic of debates in the world today include addiction, tolerance, withdrawal, physical dependence and pseudoaddiction. A condition feared by many providers in today’s world is addiction; a condition that is influenced by genetic, psychological and environmental factors that lead to compulsive use despite harm. Opiates are strong stimulants of the reward/pleasure system, increasing the level of dopamine in the system, which in turn enhances the desire to achieve the reward/pleasure. Addiction can ultimately lead to overdose and death. Tolerance, on the other hand, represents a state of adaptation in which exposure to the same amount of the drug results in a lower effect than previously obtained. Physical dependence also happens frequently and is the cause of the known withdrawal syndrome that manifests with abrupt cessation or an exaggerated reduction in the dose of opiate administered. Signs and symptoms of withdrawal include tremor, shakiness, anxiety, depression, lacrimation, rhinorrhea, fatigue, irritability, and diarrhea. Pseudoaddiction is very common in patients with SCD. It is a state, in which the patient appears to be seeking for excessive amount of medication, but is due to under-treatment of pain and resolves when the pain is treated properly. Opioid-induced hyperalgesia (OIH) results from chronic administration of opioid medications. A process that is not totally proven and well understood yet but is thought to result from a minor excitatory pathway that becomes magnified with chronic use of the opiates and, ultimately, becomes the dominant effect. The sites of pain from OIH are typically the same as the sites perceived during the VOE crisis, but the quality of the pain differs. It is more neuropathic in nature.

3.4. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the main adjuvant of opioid in today’s therapeutic guidelines of most healthcare facilities. Ketorolac tromethamine is the NSAID...
most commonly used for this purpose; it is commonly administered either intravenously or intramuscularly at a dose of 0.5 mg kg\(^{-1}\) for a maximum of 30 mg every 6 h for 5 days. NSAIDs partly inhibit the inflammatory cascade involved in VOE (see above). Although usually not sufficient to resolve a pain crisis as a sole treatment, it works synergistically with opioids. For moderate VOE pain, a single dose of 30 mg IV is typically sufficient. Opioids are limited by their propensity to cause gastritis and gastric bleeding. The drug should be used cautiously in patients with peptic ulcer disease or a history of gastrointestinal bleeding. NSAIDs can impair kidney function and accelerate the renal injury produced by sickle cell disease itself. For these reasons, many specialists avoid NSAIDs in patients with sickle cell disease.

3.5. Ketamine

Ketamine is gaining a lot of popularity for the treatment of VOE refractory to opioids. A lot of institutions have integrated its use in their algorithm of VOE treatment and strong evidence exists regarding its efficacy as an adjuvant to opioids and NSAIDs. Ketamine is a noncompetitive antagonist at the \(N\)-methyl-d-aspartate (NMDA) receptor. This property has been shown to modulate opioid tolerance and opioid-induced hyperalgesia. The use of ketamine is limited by its psychiatric side effects such as hallucinations, abnormal dreams, nightmares and abnormal behavior. Randomized controlled trials are still necessary for the regular implementation of ketamine in SCD protocols.

4. Pain management of patients with sickle cell disease with chronic and neuropathic pain

4.1. Chronic pain

In addition to the acute crises, patients with SCD also suffer from chronic pain, which often times overlap with acute pain crises and create difficulty in designing a treatment plan. These individuals can find management of their pain very difficult and therefore change providers frequently, resulting in a higher degree of misdiagnosis and misperception of their pain. Identifying the presenting syndrome can help individualize a treatment plan and therefore understanding the signs and symptoms of chronic pain is crucial for aggressive and effective therapy.

Chronic pain is generally defined as pain that is present for 3 or more months. As opposed to the acute pain, which is sharp and throbbing in nature with a sudden onset, chronic pain is often vague, deep, and achy there is present for a longer period. Approximately 5–10% of adult patients with sickle cell disease are affected with chronic pain [44]. However, a recent study from Pain in Sickle Cell Epidemiology Study reported the incidence of chronic pain in 29% of 292 adult patients [45]. These patients tend to be older and use more opioids [46]. The chronic pain is categorized into two types. The first type is objective and is due to visible signs such as leg ulcers and avascular necrosis which is associated with deep somatic pain. The second type is due to recurrent acute attacks of painful crises. Failure to treat these acute attacks can lead to chronic pain syndrome and resultant neuropathic pain. The exact
pathophysiologic mechanism is not fully understood, however central component has been described in which the threshold for the perception of pain is lowered, resulting in pain from typically nonpainful stimuli (allodynia) and severe pain generated by mildly painful stimuli (hyperalgesia) (Figure 2).

This figure depicts the age distribution of SCD patient with chronic pain. As demonstrated by the figure, the larger proportion of SCD patients with chronic pain is between 20 and 29 years old.

4.2. Pathophysiology and mechanism

Although the exact mechanism underlying the transition from acute to chronic pain is not fully understood, some contributing factors include chronic inflammation, organ damage, and opioid-induced hyperalgesia [47]. According to a study presented at the Annual Meeting of American Society of Hematology, patients with chronic pain (defined as >50% of days reported as painful crises collected over 6 months) tend to be older (41 vs. 32 years), use more opioids (11.45 mg/day vs. 2.92 mg/day), and have higher levels of mast cell activation [48].

Opioid-induced hyperalgesia is a state of sensitization caused by repetitive exposure to opioids resulting in paradoxical response to pain. Although there is no understanding or consensus on the biomolecular mechanism, it is believed to be secondary to neuroplastic changes in the central and peripheral nervous system [49]. Despite it being a controversial topic, patients with sickle cell disease with chronic pain do require increasingly higher dosage adjustments.

Recent research demonstrates clear evidence that chronic inflammation and mast cell activation plays a role in the chronic pain state of patients with sickle cell disease. Mast cells release the neuropeptide substance P, which promotes neurogenic inflammation and nociceptive

Figure 2. Distribution of SCD patient with chronic pain.
activation [48]. Additionally, tryptase, a serine proteinase found within mast cells appears far more elevated in patients with chronic pain in sickle cell disease. This can help guide future therapy directed toward inhibition of mast cell activation, and implementation of medications such as Cromolyn. This can also help identify and diagnose patients with sickle crises who present to the emergency department and are sadly mistaken as drug seeking opportunists.

4.3. Treatment/management

The cornerstone to therapy involves recognition of the disease state and assessment of the pain intensity, which helps individualize therapy. Prevention of SCD pain is crucial by avoidance of precipitating factors (dehydration, infection, diuretics, altitude, acidosis, and hypoxia), as repetitive acute inflammation can result in chronic pain. The approach to pain management in patients with SCD with chronic pain is multidisciplinary, involving the use of pharmacologic analgesic drugs, nerve blocks, physical therapy, and cognitive behavioral therapy [46]. Discussion of hydroxyurea and other disease modifying therapies is appropriate. Close attention should be made to psychosocial issues including depression and social isolation [45].

Mild chronic pain can be treated with acetaminophen or dihydrocodeine. In patients with liver failure, acetaminophen can be avoided and NSAIDS such as ibuprofen can be used, but should be used with caution in patients with borderline renal function or failure. In patients with moderate pain, consideration of slow release morphine with small amounts of rapid-release morphine for breakthrough pain is advised [46]. Alternatives to Morphine include hydromorphone, oxycodone, methadone, or transdermal fentanyl. Methadone in particular can be efficacious in patients with suspected opioid-induced hyperalgesia due to its N-methyl-D-aspartate (NMDA) antagonism and monoamine uptake reuptake inhibition. In patients who cannot tolerate opioid side effects and have contraindications the prior listed opioid analgesics, tramadol, a selective Mu-receptor agonist and serotonin–norepinephrine reuptake inhibitor can be considered [44]. The goal of chronic pain management is to maximize the quality of life rather than short-term pain suppression [45]. Other adjuvants include partial opioid agonists such as buprenorphine, topical agents, corticosteroids, antihistamines, benzodiazepines, antidepressants, anticonvulsants, and phenothiazines.

In patients with severe chronic pain, alternative procedures can be considered in addition to opioid therapy. For example, in a patient with deep somatic pain of avascular necrosis of the hip, an interventional nerve block could supply instant relief for 12 h, and potentially 72 h if the injectate is liposomal Bupivacaine [49, 50]. Physiotherapy can help strengthen muscle fibers and loosen stiff joints, preventing contractures and physical disability. Psychological support with cognitive behavioral therapy can help the patient cope with pain or deal with the mental agony and psychosocial stressors associated with sickle cell disease [46]. Adapting to cognitive skills can also help alter the perception of pain as negative thinking has been linked to higher pain scores. Massage therapy, relaxation techniques, and even self-prayer have been reported in published studies to help with chronic pain [51]. The American Pain Society strongly recommends psychological, behavioral and physical modalities as necessary complements to pharmacologic therapy, as a significant effect on pain scores and activities of daily living have been reported [52]. Orthopedic devices for back or leg support can be deployed to reduce chronic pain in the hips or back. Orthopedic surgery, such as total hip replacement should be deferred until the pain is no longer tolerable [46].
Lastly, it is important to note that patients with SCD are not immune to non-hemoglobinopathic pain. Excluding other disease processes is essential and misdiagnosis can be life threatening. Conditions that can mimic the chronic pain state include but are not limited to ischemic colitis, pancreatitis, bone marrow infarction, hepatobiliary disorders, and vertebral body necrosis [53].

4.4. Neuropathic pain

In addition to acute and chronic pain, a neuropathic component of pain plays a large and undiagnosed constituent of chronic disease. Data suggest that the development of neuropathic pain is responsible for the transition from acute to chronic pain with aging [54]. The general understanding is that multiple components of central sensitization and peripheral nerve injury are responsible. Types of neuropathic pain include peripheral neuropathic (caused by vaso-occlusive crises and neuropathies) and central neuropathic (caused by CNS damage, ictus, and central sensitization). Peripheral nerve injury and prostaglandin release can sensitize peripheral nerve endings and facilitate the transmission of pain along the A-delta and C fibers to the cerebral cortex [44]. The exact mechanism, however, is poorly understood, which hinders our progression toward achieving novel therapies.

Neuropathic pain from SCD occurs more commonly in older adults and females, which is hypothesized to be secondary to abnormalities in pain signaling pathways. These patients have extreme sensitivity to tactile touch (allodynia), increased pain from a normally painful stimulus (hyperalgesia) and extreme sensitivity to temperature [45]. Some studies demonstrate the prevalence to be approximately 20% of the chronic pain population. In a 2013 article published in Pediatric Blood and Cancer, 37% of patients with SCD were identified to have neuropathic pain and only 5% were reported to be taking a neuropathic pain drug (gabapentin), which highlights the lack of diagnosis and treatment [55]. Thus, appropriate screening tools such as the pain DETECT questionnaire could help identify patients with neuropathic pain and help initiate treatment.

4.5. Treatment/management

Although no single treatment therapy exists, a multimodal pharmacologic approach can be instituted in patients diagnosed with neuropathic pain. Treatment may include tricyclic antidepressants (TCA, SSRI, SNRIs, MAOIs) or anticonvulsants (pregabalin, gabapentin), although there is no data supporting its use in patients with SCD [56]. With a better safety profile and less side effects than opioids, tramadol (a typical analgesic with weak opioid receptor agonism and SNRI activity) can act centrally and be helpful in treating neuropathic pain, but should be used with caution in patients with renal failure [57, 58].

5. Future of SCD pain treatment

Until SCD can be fully cured (possibly with gene therapy), new and improved treatment modalities are necessary. The information currently available about SCD is that rapid and aggressive therapy at the first sign of a VOE help reduce the length of the event and even
abort it. Currently, patients with VOE receive treatment 2–3 days after the onset of the prodromal signs [16]. Measurement should be made in the future to offer patients with SCD methods of treatment available at home such as opioids (IV or IM), supplemental oxygen, and rapid hydration methods. Anti-inflammatory agents and oral opioids represent the current home treatment modalities. Vasodilators also represent a fundamental therapeutic weapon for VOE, especially when used early. Administration of nitric oxide (NO) in the emergency department has shown to abort the crisis in some patients; however, no benefit was found when NO was used during the hospital stay [59–61]. Perhaps NO could be offered as a home medication and its use would be even earlier than it would be in the ED. Recently, reports have emerged of small doses of opioid antagonist in combination with an agonist enhanced the analgesic effect and delayed the development of tolerance [62]. Recent trials targeting the inhibition of the capsaicin receptor transient receptor potential vanillin 1 (TRPV1) showed promising results in relieving pain in patients with SCD [63].

6. Conclusion

Although many complications stem from SCD, leading to a significantly reduced lifespan, pain remains the most cardinal sign of the disease and is still inappropriately treated. The main explanations for the inadequate treatment are the providers’ lack of knowledge about the disease and its narcotic requirement, lack of institutional treatment protocol in place and lack of patient education. The most important factors about the treatment, to our knowledge, are rapid and aggressive treatment as soon as signs of VOE happen, adequate rehydration and oxygenation. The treatment modalities have evolved enormously since the discovery of the disease and hopes for future treatment are bright.

Acknowledgements

To the entire staff of Advocate Illinois Masonic Medical Center, Dr. Arjang Khorasani, Dr. Kenneth Candido and Dr. Nick Knezevic, thank you for your continuous support throughout our work.

Author details

Thomas Zouki*, Armen Haroutunian and Tennison Malcolm

*Address all correspondence to: zoukit7@gmail.com

Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, Illinois, USA
References

[1] Regional Committee for Africa 60. S-Cell Disease: A strategy for the WHO African Region. 2011 May 26 [cited 2018 Apr 28]. Available from: http://apps.who.int/iris/handle/10665/1682

[2] Bender MA. Sickle Cell Disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2018 Apr 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK13777/

[3] Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: An increasing global health problem. Bulletin of the World Health Organization. 2001;79(8):704-712

[4] CDC. Data and Statistics | Sickle Cell Disease | NCBDDD | CDC [Internet]. Centers for Disease Control and Prevention. 2016 [cited 2018 Apr 30]. Available from: https://www.cdc.gov/ncbddd/sicklecell/data.html

[5] Diallo D, Tchernia G. Sickle cell disease in Africa. Current Opinion in Hematology. 2002 Mar;9(2):111-116

[6] Scott RB. Health care priority and sickle cell anemia. JAMA [Internet]. 1970 Oct 26 [cited 2018 Apr 7];214(4):731-734. Available from: https://jamanetwork.com/journals/jama/fullarticle/357392

[7] Ballas SK. Update on pain management in sickle cell disease. Hemoglobin [Internet]. 2011 Oct 1 [cited 2018 Apr 5];35(5-6):520-529. Available from: https://doi.org/10.3109/036330269.2011.610478

[8] Frenette PS. Sickle cell vaso-occlusion: Multistep and multicellular paradigm. Current Opinion in Hematology. 2002 Mar;9(2):101-106

[9] Ballas SK. Current issues in sickle cell pain and its management. Hematology. American Society of Hematology. Education Program. 2007;1:97-105

[10] Plankton S, Haywood C, Segal JB, Dover GJ. Hospitalization rates and costs of care of patients with sickle-cell anaemia in the state of Maryland in the era of Hydroxyurea. American Journal of Haematology [Internet]. 2006 Dec 1 [cited 2018 Apr 4];81(12):927-932. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.20703

[11] Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. American Journal of Hematology [Internet]. 2005 May 1 [cited 2018 May 23];79(1):17-25. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.20336

[12] AlJuburi G, Laverty AA, Green SA, Phekoo KJ, Bell D, Majeed A. Socio-economic deprivation and risk of emergency readmission and inpatient mortality in people with sickle cell disease in England: observational study. Journal of Public Health (Oxford, England)
[Internet]. 2013 Dec 1 [cited 2018 May 23];35(4):510-517. Available from: https://academic.oup.com/jpubhealth/article/35/4/510/1686557

[13] Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease: Cooperative study of sickle cell disease. Blood. 15 Jul 1995;86(2):776-783

[14] Powars DR. Natural history of sickle cell disease—The first ten years. Seminars in Hematology [Internet]. 1975 Jul 1 [cited 2018 May 23];12(3):267-285. Available from: https://www.seminhematol.org/article/0037-1963(75)90021-9/fulltext

[15] Jenkins TL. Sickle Cell Anemia in the Pediatric Intensive Care Unit: Novel Approaches for Managing Life-threatening Complications. AACN Advanced Critical Care [Internet]. 2002 May 1 [cited 2018 Apr 7];13(2):154-168. Available from: http://acc.aacnjournals.org/content/13/2/154

[16] Ballas SK, Gupta K, Adam-Graves P. Sickle cell pain: A critical reappraisal. Blood. August 2012;120(18):3647-3656

[17] Beyer JE, Simmons LE, Woods GM, Woods PM. A chronology of pain and comfort in children with sickle cell disease. Archives of Pediatrics & Adolescent Medicine [Internet]. 1999 Sep 1 [cited 2018 Apr 7];153(9):913-920. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/347703

[18] Jacob E, Beyer JE, Miaskowski C, Savedra M, Treadwell M, Styles L. Are there phases to the Vaso-occlusive painful episode in sickle cell disease? Journal of Pain and Symptom Management [Internet]. 2005 Apr 1 [cited 2018 Apr 7];29(4):392-400. Available from: http://www.jpsmjournal.com/article/S0885-3924(05)00050-3/abstract

[19] Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. Blood. 1992;79(8):2154-2163

[20] Jacob E, Mueller BU. Pain experience of children with sickle cell disease who had prolonged hospitalizations for acute painful episodes. Pain Medicine. 2008;9:13-21

[21] A Brief History of Sickle Cell Disease [Internet]. [cited 2018 Apr 30]. Available from: http://www.sicklecell.howard.edu/ABriefHistoryofSickleCellDisease.htm

[22] Diggs LW, Ching RE. Pathology of sickle cell anemia. Southern Medical Journal [Internet]. 1934 Oct 1 [cited 2018 Apr 30];27(10):839-845. Available from: https://insights.ovid.com/southern-medical/smeda/1934/10/000/pathology-sickle-cell-anemia/3/00007611

[23] Diggs LW, Williams DL. Treatment of Painful Sickle Cell Crises with Papaverine: Preliminary Report. Southern Medical Journal [Internet]. 1963 [cited 2018 Apr 30];56(5):472-474. Available from: https://www.cabdirect.org/cabdirect/abstract/19632901722

[24] Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. New England Journal of Medicine [Internet]. 2000 Jun 22 [cited 2018 May 23];342(25):1855-1865. Available from: https://doi.org/10.1056/NEJM200006223422502
[25] Hassell KL, Eckman JR, Lane PA. Acute multiorgan failure syndrome: A potentially catastrophic complication of severe sickle cell pain episodes. The American Journal of Medicine [Internet]. 1994 Feb 1 [cited 2018 May 23];96(2):155-162. Available from: http://www.sciencedirect.com/science/article/pii/0002934394901368

[26] Ngo S, Bartolucci P, Lobo D, Mekontso-Dessap A, et al. Causes of death in sickle cell disease adult patients: Old and new trends. Blood [Internet]. 2014 Dec 6 [cited 2018 May 23];124(21):2715. Available from: http://www.bloodjournal.org/content/124/21/2715

[27] De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle-cell disease. Lancet. 1982 Jul 31;2(8292):229-231

[28] Ballas SK. Pain Management of Sickle Cell Disease. Hematology/Oncology Clinics of North America [Internet]. 2005 Oct [cited 2018 Apr 28];19(5):785-802. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0889858805000894

[29] Gaston MH, Verter JJ, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. The New England Journal of Medicine. 1986 Jun 19;314(25):1593-1599

[30] Okomo U, Meremikwu MM. Fluid replacement therapy for acute episodes of pain in people with sickle cell disease. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2017 [cited 2018 May 23]. Available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD005406.pub5/full

[31] Friedland LR, Pancioli AM, Duncan KM. Pediatric emergency department analgesic practice. Pediatric Emergency Care. 1997;13:103-106

[32] Brown DW. The dawn of healthy people 2020: A brief look back at its beginnings. Preventive Medicine. 2009;48:94-95

[33] Aisiku IP, Penberthy LT, Smith WR, et al. Patient satisfaction in specialized versus nonspecialized adult sickle cell care centers: The PiSCES study. Journal of the National Medical Association. 2007;99:886-890

[34] Ballas SK. Ethical issues in the management of sickle cell pain. American Journal of Hematology. 2001;68:127-132

[35] Jacob E, Miaskowski C, Savedra M, et al. Management of vaso-occlusive pain in children with sickle cell disease. Journal of Pediatric Hematology/Oncology. 2003;25:307-311

[36] Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise [Internet]. 2007 [cited 2018 May 23]. Available from: https://www.jci.org/articles/view/30920/pdf

[37] Maxwell K, Streetly A, Bevan D. Experiences of hospital care and treatment-seeking behavior for pain from sickle cell disease: Qualitative study. The Western Journal of Medicine. 1999;171:306-313

[38] Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. Annals of Emergency Medicine. 2004;43:494-503
[39] Sickle cell disease: Managing acute painful episodes in hospital. Guidance and guidelines. NICE [Internet]. [cited 2018 Apr 28]. Available from: https://www.nice.org.uk/guidance/cg143/chapter/1-recommendations

[40] Ballas SK, McCarthy WF, Guo N, et al. Early detection of response to Hydroxyurea therapy in patients with sickle cell Anemia. Hemoglobin [Internet]. 2010 Oct [cited 2018 Apr 29];34(5):424-429. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20854115

[41] Ballas SK, Bauserman RL, McCarthy WF, et al. Utilization of analgesics in the multicenter study of hydroxyurea in sickle cell anemia: Effect of sex, age, and geographical location. American Journal of Hematology 2010 Aug;85(8):613-616

[42] Brookoff D, Polomano R. Treating sickle cell pain like Cancer pain. Annals of Internal Medicine. 1992 Apr;116:364-368

[43] Miller ST, Kim HY, Weiner D, et al. Inpatient management of sickle cell pain: A ‘snapshot’ of current practice. American Journal of Hematology. 2012;87:333-336

[44] Niscola P, Sorrentino F, Scaramucci L, De Fabritiiis P, Cianciulli P. Pain syndromes in sickle cell disease: An update. Pain Medicine [Internet]. 2009 Apr 1 [cited 2018 May 1];10(3):470-480. Available from:https://academic.oup.com/painmedicine/article/10/3/470/1929112.

[45] Chen E, Cole SW, Kato PM. A review of empirically supported psychosocial interventions for pain and adherence outcomes in sickle cell disease. Journal of Pediatric Psychology. 2004 May;29(3):197-209

[46] Okpala I, Tawil A. Management of pain in sickle-cell disease. Journal of the Royal Society of Medicine [Internet]. 2002 Sep [cited 2018 May 1];95(9):456-458. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1279994/

[47] Pope M, Albo C, Kidwell KM, Xu H, Bowman L, Wells L, et al. Evolution of chronic pain in sickle cell disease. Blood [Internet]. 2016 Dec 2;128(22):1297. Available from: http://www.bloodjournal.org/content/128/22/1297.abstract

[48] Tennant F, MD, DrPH, Ciccone TG. New look at sickle cell patients with chronic pain [Internet]. Practical Pain Management. [cited 2018 May 1]. Available from:https://www.practicalpainmanagement.com/resources/news-and-research/new-look-sickle-cell-patients-chronic-pain

[49] Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011 Apr;14(2):145-161

[50] Commissioner of the FDA. FDA In Brief: FDA approves new use of Exparel for nerve block pain relief following shoulder surgeries [Internet]. [cited 2018 May 1]. Available from: https://www.fda.gov/NewsEvents/Newsroom/FDAINBrief/ucm604021.htm

[51] Myers DC, Robinson EM, Guthrie HT, Lamp PS, Lottenberg R. Adjunctive approaches for sickle cell chronic pain. Complementary Health Practice Review. 1999 Dec 1;5:203-212

[52] Pain in Sickle-Cell Disease Guideline. APS [Internet]. [cited 2018 May 1]. Available from: http://americanpainsociety.org/education/guidelines/sickle-cell-guideline
[53] Al-Salem AH, Naserullah Z, Qaisaruddin S, Al-Abkari H, Al-Faraj A, Yassin YM. Splenic complications of the sickling syndromes and the role of splenectomy. J Pediatr Hematol Oncol [Internet]. 1999 [cited 2018 May 1];21(5):401-406. Available from: http://europepmc.org/abstract/med/10524454

[54] Fillingim RB. Individual differences in pain responses. Current Rheumatology Reports [Internet]. 2005 Sep 1 [cited 2018 May 23];7(5):342-347. Available from: https://link.springer.com/article/10.1007/s11926-005-0018-7

[55] Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. Pediatric Blood & Cancer. 2014 Mar;61(3):512-517

[56] Parikh RH. Patient-controlled analgesia improves pain control in a vaso-occlusive crisis in sickle cell patients. Clinical Research in Practice: The Journal of Team Hippocrates [Internet]. 2017 Sep 14 [cited 2018 May 1];3(2). Available from: http://digitalcommons.wayne.edu/crp/vol3/iss2/10

[57] Hollingshead J, Dühmke RM, Cornblath DR. Tramadol for neuropathic pain. Cochrane Database of Systematic Reviews. 2006 Jul 19;3:CD003726

[58] Stamer UM, Stüber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesthesia & Analgesia [Internet]. 2008 Sep [cited 2018 May 23];107(3):926. Available from: https://journals.lww.com/anesthesia-analgesia/pages/articleviewer.aspx?year=2008&issue=09000&article=00035&type=Fulltext

[59] Gladwin MT, Kato GJ, Weiner D, Onyekwere OC, Dampier C, Hsu L, et al. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: A randomized controlled trial. JAMA [Internet]. 2011 Mar 2 [cited 2018 Apr 30];305(9):893-902. Available from: https://jamanetwork.com/journals/jama/fullarticle/645928

[60] Lopez BL, Davis-Moon L, Ballas SK, Ma X. Sequential nitric oxide measurements during the emergency department treatment of acute vaso-occlusive sickle cell crisis. American Journal of Hematology [Internet]. 2000 May 1 [cited 2018 May 23];64(1):15-19. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.10852

[61] Head CA, Swerdlow P, McDade WA, et al. Beneficial effects of nitric oxide breathing in adult patients with sickle cell crisis. American Journal of Hematology [Internet]. 2010 Oct 1 [cited 2018 Apr 30];85(10):800-802. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.21832

[62] Crain SM, Shen K-F. Antagonists of excitatory opioid receptor functions enhance morphine’s analgesic potency and attenuate opioid tolerance/dependence liability: Pain [Internet]. 2000 Feb [cited 2018 Apr 30];84(2):121-131. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=0006396-20002010-00002

[63] Hillery CA, Kerstein PC, Vilceanu D, et al. Transient receptor potential vanilloid 1 mediates pain in mice with severe sickle cell disease. Blood [Internet]. 2011 Sep 22 [cited 2018 Apr 30];118(12):3376-3383. Available from: http://www.bloodjournal.org/content/118/12/3376
