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Management of Opioid Use Disorder in Sickle Cell Anaemia amidst Growing Menace in the General Population

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Abstract

Nigeria has a very high number of sickle cell disease (SCD) population with addition of 150,000 babies born annually with the disease. Early infant diagnosis and good care make many of these babies survive to adulthood. Severe pain requiring moderately strong or very strong analgesics is a common presentation of patients with Sickle Cell Anaemia. Paediatricians find ready usefulness of Opioids which are very useful for the painful episodes among these patients. Therefore, the chances of abuse and addiction to these medications become very high and constitute additional burden on the deficient manpower in the health sector. Opioid Use Disorder among Sickle Cell Disease patients has subtle presentation, so a high index of suspicion is required to make both the diagnosis and referral to treatment centres. In this review, the epidemiology, pain pathophysiology, behavioural and pharmacologic therapy have been re-examined.

Keywords

Sickle Cell Disease, Opioid Use Disorder, Global Menace, Treatment Centres, True Addiction and Pseudo-Addiction

1. Introduction

Sickle cell disease (SCD) is a spectrum of genetic illness characterised by the presence of two abnormal Haemoglobins one of which is Haemoglobin S (HbS) in an affected individual. The homozygous inheritance of two abnormal Haemoglobin S results in Sickle cell anaemia (SCA). Sickle cell anaemia produces chronic haemolytic anaemia, microvascular occlusion, recurrent ischaemic pain,

tissue infarction, organ damage and decreased quality of life. The abnormal haemoglobin S undergoes polymerization in deoxygenated condition leading to erythrocytes with rigid membrane, abnormally shaped and fragile leading to haemolysis, hyperviscosity and occlusion of the microvasculature. Occlusion of blood vessels by irreversible sickled red cells leads to the main pathologic mechanism of SCD known as vaso-occlusive crises presenting as severe pain in affected individuals. [1]

Individuals affected by sickle cell crises have recurrent severe bone pains which often require hospitalization and use of opioid medications to control. Some acute and chronic complications of sickle cell disease such as chronic osteomyelitis, avascular necrosis and leg ulcers can also lead to chronic pain requiring prolonged use of opioids.

With the increasing concern about drug abuse worldwide, patients with sickle cell disease are also prone to developing dependence and addiction like others in the general populace since the condition is lifelong and affected individuals will usually require opioids analgesics to manage their acute pain episodes or chronic pain conditions. In addition, poorly controlled pain, unregulated access to controlled substances, ignorance, personal or family history of substance abuse, poor mental health status and some other factors can predispose an individual with SCD to developing opioid use disorder.

It is therefore important that physicians who are involved in the care of the adolescent and young adults with sickle cell recognise the need for early identification and referral of patients at risk of opioid use disorder.

2. Case Review

A.B. was a 17-year-old female diagnosed with sickle cell anaemia in childhood. Her routine medications included Folic acid, Vitamin C and Proguanil. She did not attend routine clinic follow up regularly and her stable state packed cell volume (PCV) was unknown. She has had 4 episodes of moderate to severe vasoocclusive crises requiring presentation at the emergency unit in the last 6 months. During the last admission, she was managed for acute osteomyelitis and septic arthritis of the left shoulder and left knee. Additional history taken then revealed that she has been enrolled as a trainee at a patent medicine store where she has been taught how to administer intramuscular injections to clients and she also confidently injected herself. She admitted injecting herself with injectable paracetamol but denies administering opioids even though she knows about opioids, particularly pentazocine. She also had access to a patent medicine trainee colleague who gives her intramuscular injections such as diclofenac, whenever she has pain at home.

She was noticed to have unrelenting pain despite being on oral Morphine at 10mg given 4 hourly and intramuscular pentazocine 30 mg given as required for breakthrough pain. Her pain "subsided" when given water for injection placebo. Placebo was given intermittently to her whenever she complained of pain and

requested for analgesia. Opioid use disorder (OUD) was suspected. The risk factors identified in her raised suspicion for OUD. These risk factors included; increasing frequency of vaso-occlusive crises, pain from osteomyelitis and septic arthritis, access to opioid medication in a patent medicine store, knowledge and practice of injecting herself and others and response of her pain to placebo for analgesia. She was counselled on the potential dangers of indiscriminate drug use and dangers of self-medication including self-injection. The patient and her parents were also counselled about the need to commence Hydroxyurea and discharged to follow up clinic.

Even though our patient did not admit to injecting Opioid medications, we were concerned mainly because she was a SCA patient who has started injecting herself on the thigh with other drugs and being a patent medicine store apprentice with knowledge and indiscriminate access to opioids like pentazocine. Thorough evaluation should involve clinicians exploring all the important aspect of history and then take proactive measures in the prevention of substance use disorder among patients with SCD.

3. Pathogenesis of Pain in Sickle Cell Disease

The central pathogenetic mechanism causing painful episodes in patients with SCD is due to occlusion of the microvascular circulation (arterioles and capillaries) by rigid sickled red cells that have adhered to vascular endothelium leads to ischaemia and infarction; Figure 1. The resulting tissue injury and inflammation leads to the release of chemical mediators such as bradykinin, prostaglandins,

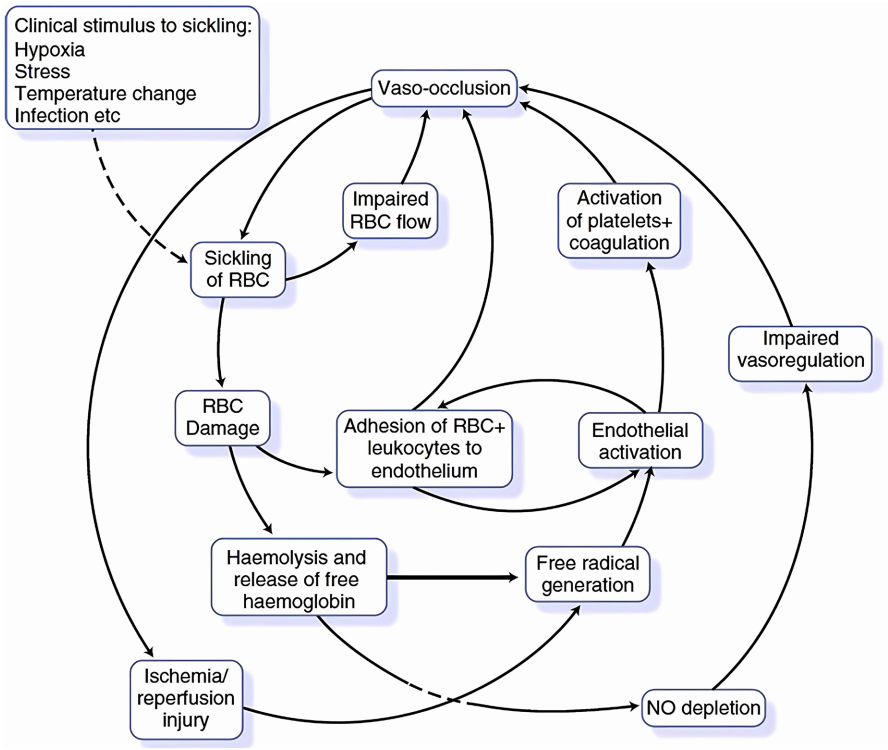

Figure 1. Mechanism of Vaso-occlusion leading to painful crisis in Sickle Cell Anaemia.

substance P and others that stimulates nociceptive fibres which then transmit the impulses to the central nervous system. [2] [3]

Pain in SCA can be classified as nociceptive, neuropathic, mixed and breakthrough pain. It has also been described as progressing through 4 distinct stages including the prodromal phase during which numbness or paraesthesia can develop at pain site, initial infarct phase during which the pain progressively worsens and peaks, post infarct phase during which pain persist with signs of inflammation and the resolution phase characterised by progressive reduction of pain. However, there is much variability in the onset, progression and intensity of painful episodes. [2] [3] SCD pain is multidimensional and can be acute recurrent pain that last less than 3 - 6 months or chronic pain lasting for more than 6 months. [4]

4. Epidemiology of Opioid Use Disorder (OUD) in the General Population

Drug abuse is an emerging public health threat with an increasing trend of drug use recorded globally. According to a 2019 United Nations drug report, an estimated 271 million people corresponding to about 5.5% of the world population aged 15 - 64 years used drug in 2018. About 53 million of these used opioids. An estimated 35 million people are suffering from drug use disorder globally. [5] In 2019, Half a million people died from drug use with 70% of these deaths related to opioid use and between 2010 and 2019, the global number of opioid users doubled globally. Although there is an increase in drug use globally, there is still a disparity in the available doses of opioids available for pain relieve for patients that require it for pain relief. [6] [7]

This increasing trend of drug abuse is also seen in Nigeria. A nationwide drug use survey done in Nigeria in 2017 estimated drug use prevalence in Nigeria to be 14.4% corresponding to about 14.3 million people aged between 15 - 64 years, 20% of these individuals are estimated to have a drug use disorder. Opioids (Tramadol, codeine and morphine) were implicated in 4.7% of this population corresponding to about 4.6 million people who used opioids for non-medical purposes and nearly 0.1% of the adult population injects drugs. [8] A study conducted in four southwestern Universities in Nigeria found a drug and substance use prevalence of 45.7% (alcohol and cigarette inclusive) with tramadol and codeine syrup being the most misused drugs. [9] OUD is common among the adolescent population because of the neuroplasticity of their brain and the under-development of the prefrontal cortex which is necessary for developing self-control. [10]

Patients with chronic pain are at risk of developing opioid use disorder due to prolonged exposure to opioid medications. A study done to assess the prevalence of opioid use disorder among patients receiving long term opioid therapy for non-cancer pain found the lifetime prevalence of any opioid use disorder (OUD) to be 41.3% (28.1% for mild OUD, 9.7% for moderate OUD, and 3.5% for severe OUD). [11]

5. Epidemiology of Opioid Use Disorder (OUD) among Sickle Cell Disease Population

Generally, sickle cell disease patients are not considered to be at an increased risk of opioid use disorder than the general population. Despite the increasing prevalence of opioid use disorders globally, the prevalence of opioid use disorder among sickle cell disease patients appears to be low although comprehensive local data is lacking in Nigeria [4] [12]. However, because of the increase in the prevalence of opioid use disorder to epidemic proportions in the general populace, there is a growing concern that the prevalence of OUD can also increase in patient with chronic pain who have reasons to require opioids in the management of their conditions. [10] [11]

A cohort study done to characterize opioid utilization among 3882 SCD patient in the United States, found that 23% of adult SCD and 3% of paediatric SCD patients used more than 30 mg of oral morphine equivalent daily. [13] Another study conducted to determine aberrant opioid behaviour among adolescent and young adults being managed for haematology/oncologic condition found that 11.7% of those using opioids for their condition exhibited aberrant opioid behaviour such as; demanding more medications, obtaining prescriptions from multiple sources and use of drugs to feeling good). [14]

Bazuaye *et al.* conducted a study to assess opioid dependence among adult SCD patient in Benin and reported a prevalence of 17.1%, while another study assessing the prevalence of substance use disorder among adult SCD patient reported a prevalence of 5% and most of the substances used were opioids. [15] [16] There have also been several case reports and series of OUD especially pentazocine among the SCD individuals including the paediatric population. [17] [18] [19]

There are some specific risk factors that can predispose SCD patients to prolong use of opioid and dependence. These risk factors includes poorly controlled pain crises, chronic pain due to chronic osteomyelitis, avascular necrosis, pathologic fractures, uncontrolled access to medications, genetic predisposition, poor family or social support, being a health worker or being affiliated to a health worker, ignorance about side effects of the drugs, concurrent mental health disorders and family history of mental illness or substance use disorder. [14] [17]

Since opioids form the mainstay of management of severe vasoocclusive episodes, there are always concerns about the effects of prolonged use of opioids including tolerance—in which increasingly higher doses are required to produce the same pharmacologic effect, physical dependence—in which continual usage of the drug is required for biologic functioning and opioid induced hyperanalgesia (OIH) in which the experience of pain is amplified because of the sensitization of the nociceptive pathways. [20] The use of short acting opioids such as pentazocine mainly in Nigeria contributes to these concerns as it has a short half-life and can predispose the patient seeking more doses to relieve their pain.

6. Mechanism of Action of the Opioid Analgesics

Opioid analgesics bind to the opioid receptors located in the brain. There are five types of opioid receptors which are mu, kappa, delta, nociception receptor and zeta receptors. [21] The binding of opioid to the μ-opioid receptors located around the areas of the brain responsible for pain perception (thalamus, cingulate cortex, periaqueductal grey area and insula), in the dorsal horn of the spinal cord and the peripheral nerves leads to pain relief. However, these same receptors are also located in the mesolimbic reward regions of the brain (ventral tegmental area and nucleus accumbens) and causes euphoria by inhibiting the inhibitory pathways of dopamine release. The μ-receptors located in the other brain region such as the brainstem and the gastrointestinal tract is responsible for other side effects of opioids like respiratory depression and constipation. [10] [22]

The repeated use of opioids leads to conditioning—a learned association between use of drug and the drug effects of analgesia and pleasure. These learned associations are strengthened with prolonged and increasing use and over time craving for the drug effects develop. [10] Thus opioid addiction develops through a change in the neurophysiology of the brain.

7. Management of Opioid Use Disorder in Sickle Cell Disease Patients

The management of opioid use disorder in patients with sickle cell disease presents a unique challenge and a multidisciplinary team (MDT) consisting of Haematologists (Paediatric and adult), psychiatrists, psychologist, pain or palliative care specialist and all other relevant specialists is required for optimal care of these patients. The MDT team will be important in drawing up a comprehensive care plan that will ensure a holistic approach to care of SCD patients. The initial assessment for OUD among SCD patients follows a **SBIRT** (Screening, Brief intervention and Referral to treatment) model which is a comprehensive, integrated, public health approach to the delivery of early intervention and treatment services for persons at risk or persons with substance abuse disorders and according to the American Academy of Paediatrics can also be used as a model to initially screen adolescents. The SBIRT goal is to define substance use along a spectrum ranging from abstinence to addiction and plan appropriate intervention suitable for the clinical situation. [23] [24]

7.1. Screening

Standardized screening tools can be used to identify patients that are at risk of opioid use disorder. There are various types of validated screening tools, examples include the **S2BI** (screening to brief intervention) which assesses how often a patient has used opioids and other substances of abuse in the past year with the patient required to answer on the frequency with responses like never, once or twice, monthly and weekly or more. The **S2BI** tool is very sensitive and specific

and can detect various clinically relevant substance use risk level corresponding to the Diagnostic and statistical manual fifth edition (DSM-5) classification of SUD. [23] A study done to determine the validity of the S2BI screening tool among adolescents found that it had a sensitivity of 90% and specificity of 83% in identifying a past-year SUD, and a sensitivity of 90% with specificity of 91% in identifying severe SUD. [25] Similarly, the **BSTAD** (Brief screener for tobacco, alcohol and other drugs), another screening tool validated for use in the adolescent population has a sensitivity and specificity of 80% and 90% respectively in detecting marijuana and other illicit drug use. [26]

7.2. Brief Intervention

The result of the screening tool determines the brief intervention done for the patient. Patients who have never used any substance or drugs are counselled and educated on the dangers of drug abuse with positive reinforcements provided for their healthy lifestyle choices in an effort to delay initiation of drug misuse. Patients with opioid use without disorder who use the drug occasionally are advised to stop and counselled on the medical harms associated with substance use, they are also followed up to ensure that opioid misuse is not worsening. Patients with mild-moderate OUD are also counselled and advised to stop, referral to a substance abuse specialist should be considered if there are difficulties in reducing use and motivational interviewing technique should be used if patient is ambivalent about engaging with treatment. All patients with severe OUD based on the screening should be referred promptly to an addiction specialist where patient can be fully evaluated, offered medically supervised withdrawal therapy and rehabilitation.

7.3. Referral to Treatment Centre

A full evaluation is required to identify the predisposing factors, genetic or environmental influences that can predispose to drug use in patients with SCD. Also, concomitant mental health illness such as depression that can worsen drug use can be identified and treated. Opioid use disorder can be diagnosed using the Diagnostic and Statistical manual fifth edition (DSM-5) criteria that consist of eleven symptoms in four categories. Depending on the number of symptoms identified in the patient, OUD can be divided into mild (2 - 3 symptoms), moderate (4 - 5 symptoms) and severe (≥6 symptoms) opioid use disorder. [27] Patients are offered outpatient care or residential care depending on the specific clinical scenario and severity of opioid use disorder. Outpatient care can be conducted as individual therapy, family therapy and group therapy. Care could also be conducted as an intensive outpatient program or partial hospitalization program. [24] A residential treatment program last for about 3 - 6 months in a designated area within an hospital that also has other features as close to the home environment as possible. Patients undergo medically supervised withdrawal and rehabilitation therapy and other aspect of care including medical, nutritional and others are provided. Therapeutic boarding school is a type of

care facility that combines rehabilitation with educational and vocational training to avoid disruptions during the admission period, however this is not available in Nigeria. [23] [24]

8. Behavioural Interventions

8.1. Cognitive Behavioural Therapy

Cognitive behavioural therapy is a type of psychotherapeutic treatment that helps individuals identify and change destructive or disturbing thought patterns that have a negative influence on their behaviour and emotion. It focuses on monitoring thoughts, feelings, and cues that that triggers drug use. CBT teaches people to anticipate problems and develop effective coping strategies. Apart from being useful in managing opioid use disorder, CBT can also be used as a non-pharmacologic strategy for coping with pain in SCD. [20] [24]

8.2. Contingency Management

Individuals are rewarded or reinforced for evidence of positive behavioural change. Low-cost incentives are given in exchange for participating in treatment, achieving important goals and for maintaining abstinence. [24]

8.3. Motivational Enhancement Therapy

Motivational enhancement therapy is a counselling approach designed to help individuals find the motivation to make positive change. It is based on the concept that a person becomes more motivated to change once they see the mismatch or discrepancy between their current status and their goals. [24]

8.4. Adolescent Community Reinforcement Approach

This approach focuses on helping the adolescent abstain from drugs by replacing influences that reinforces drug use with healthier family, social and educational or vocational reinforcers. It uses other important people in the life of the adolescent to reinforce change. [24]

8.5. Pharmacologic Agents Used in Management

Opioid substitution therapy (OST) involves using longer acting opioid receptor agonist that binds to opioid receptors, alleviate withdrawal symptoms and reduces craving and drug seeking behaviour. Drugs like methadone (opioid agonist) and Buprenorphine (mixed opioid agonist-antagonist) have been shown to be effective in the adolescent population. [24]

Naltrexone (an opioid receptor antagonist) is also used to treat Opioid use disorder. The patient must have been detoxified before commencing naltrexone to prevent precipitation of severe withdrawal symptoms.

9. Disease Modifying Therapies

Disease modifying therapies like Hydroxyurea can help improve the overall

clinical state of SCD affected individuals. Increased foetal haemoglobin (HbF) was found to be associated with a less severe phenotype of SCD and this made induction of foetal haemoglobin a mainstay of disease modifying therapy of sickle cell disease. Hydroxyurea increases the HbF fraction of the Haemoglobin and prevents sickling because it does not interact with HbS polymers. It also improves RBC hydration thus preventing cellular dehydration that can lead to sickling. The documented laboratory effect of Hydroxyurea includes increased haemoglobin, increased Mean Corposcular Volume (MCV). Hydroxyurea also decreases the total leucocytes, absolute neutrophil count, platelet and reticulocyte count. It has been demonstrated to have clinical benefits of reducing the number of vasoocclusive crises, reduces episodes of life-threatening acute chest syndrome, reduces transfusion needs and hospitalizations. It also helps to delay the progression to chronic organ damage. These clinical and laboratory benefits of hydroxyurea were also demonstrable in children such that infants can be commenced on Hydroxyurea. [28] [29] [30] Even though the routine use of Hydroxyurea is advocated, the use in Nigeria is still hampered by affordability, awareness, patient and caregiver preferences and the concerns about potential complications resulting from long term use.

Crinzalizumab is a P-selectin inhibitor that is administered intravenously to patients with sickle cell disease as the upregulation of P-selectin in endothelial cells and platelets contribute to the pathogenesis of vasoocclusion and bone pain crises. Patients who received crinzalizumab had less frequent crises compared to patients who received placebo in a randomized controlled trial. [31]

Voxelotor, an oral haemoglobin S polymerization inhibitor acts by binding reversibly to haemoglobin, stabilizing it in the oxygenated state and preventing polymerization provoked by deoxygenated haemoglobin S. This leads to reduced sickling, reduced viscosity and prevents haemolysis. Voxelotor can be used in children aged 4 years and above. Among the paediatric group patients who received voxelotor in the HOPE-KIDS 1 trial, 47% had >1 g/dl (gram per decilitre) increase in haemoglobin concentration from baseline by week 24, 35% had >1.5 g/dl increase and 21% had >2.0 g/dl increase with reductions in levels of indirect bilirubin, lactate dehydrogenase and percentage reticulocytes which are all markers of haemolysis. [32] [33]

Crinzalizumab and voxelotor has been approved by the Food and Drug administration in the United States [31] [34] but is yet to be widely available for use in Nigeria. These novel agents will improve the quality of life of SCD patients and reduce the frequency of vasoocclusive crises and need for opioid analgesics.

10. The Dilemma: True Addiction and Pseudo-Addiction in Sickle Cell Disease

While addiction is a chronic relapsing neurobiopsychoscocial disorder that is characterised by an impaired ability to control drug use and continued use de-

spite problems, the aberrant drug seeking symptoms displayed by an addicted person can also be exhibited by some patients with SCD especially when their pain is poorly controlled, a phenomenon known as pseudo-addiction. The recurrent unpredictable acute painful episodes experienced by SCD patients that often require multiple hospitalizations and opioid analgesia for pain relief makes them vulnerable to bias or being labelled as an addict by medical staff. This is even more so as the experience of pain is subjective and there may be no objective clinical or radiological sign that health care staff can use to grade pain severity in these group of patients in the acute settings.

Pseudo-addiction occurs when there is poor pain control and the behaviour exhibited in response to this pain undermanagement is used as evidence for diagnosis of addiction. Pseudo-addiction is a cycle that is postulated to progress through three phases. First, when "as needed" dosing of inadequate doses of pain medication is prescribed for continuous pain, patient starts to requests for additional doses of analgesics. Then, when these requests are ignored, the patient tries to convince the healthcare staff of their pain severity by moaning, crying or writhing in pain. These behaviours are interpreted by the healthcare staff as aberrant and drug seeking and they refuse to escalate the dose of analgesics. Finally, this progresses to a crises phase during which the patient increases the level of bizarre drug seeking behaviour. This cycle continues with the patient seeking to acquire drugs and the physician refusing to treat pain resulting in a lack of trust between the two parties and ultimately the patient can be mislabelled as a drug addict. [2]

Pseudoaddiction can be distinguished from true addiction by the resolution of aberrant behaviour and return to normal functioning once pain is adequately controlled. It is therefore important that painful episodes in SCD patients be promptly and adequately treated to reduce drug seeking behaviours and to reduce suffering that can lead to depression which can also predispose to substance or opioid misuse. Sickle cell patients are often dissatisfied about their treatment in the emergency department and complain that pain management is not optimal and they often face discrimination from health care workers and risk being labelled drug seeking. A retrospective review of one emergency room practice shows that the time to initial analgesic administration was still longer significantly than what is recommended by pain management guidelines (15 minutes from time of entering the Emergency Department). [35] Health care workers have been shown to overestimate the prevalence of opioid misuse among SCD patients [36]

True addiction on the other hand is usually opioid use not related to pain control and patient can exhibit behaviours including self-administration of opioids in increasing doses, stealing of prescription pads, visiting multiple physicians and so on. [2] [19]

Another area that could pose a challenge for physicians is distinguishing between a vasoocclusive episode and opioid induced hyperalgesia which occurs in patients who have been on chronic opioid use. Opioid induced analgesia occurs

due to nociceptive sensitization resulting in patient becoming paradoxically more sensitive to certain painful stimuli. [37]

11. Conclusion and Recommendations

Sickle cell disease patients represent a model condition in which the challenges of pain management are fully expressed. Physicians managing vasoocclusive crises are often faced with a dilemma of how to relieve suffering without enabling addiction. A multidisciplinary team consisting of haematologists, pain care specialists and behavioural scientists will be useful in distinguishing a patient in sickle cell crisis who needs aggressive pain control plan and a SCD patient with opioid use disorder requiring treatment. [2] [22] [38] [39] Standardized clinical practice guidelines with recommendation for pain management in the acute setting can be developed both locally and nationally. The use of opioid sparing pain strategies for chronic pain such as regional nerve block can also be explored. [40] Patients and their parents should be educated on the dangers of misuse of prescription opioids and national guidelines regulating access to controlled substances should be implemented. SCD patients should also be screened for risk of opioid misuse using standardized screening tools prior to commencement of long-term opioid therapy and they should also be screened for opioid use disorder periodically as part of their routine care plan.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Gardner, R.V. (2018) Sickle Cell Disease: Advances in Treatment. *Ochsner Journal*, **18**, 377-389. https://doi.org/10.31486/toj.18.0076

[2] Geller, A.K. and O'Connor, M.K. (2008) The Sickle Cell Crisis: A Dilemma in Pain Relief. *Mayo Clinic Proceedings*, **83**, 320-323. https://doi.org/10.4065/83.3.320

[3] Wright, J. and Ahmedzai, S.H. (2010) The Management of Painful Crisis in Sickle Cell Disease. *Current Opinion in Supportive and Palliative Care*, **4**, 97-106. https://doi.org/10.1097/SPC.0b013e328339429a

[4] Ruta, N.S. and Ballas, S.K. (2016) The Opioid Drug Epidemic and Sickle Cell Disease: Guilt by Association. *Pain Medicine*, **17**, 1793-1798. https://doi.org/10.1093/pm/pnw074

[5] United Nations Office on Drugs and Crime (2019) Executive Summary. https://wdr.unodc.org/wdr2019/en/exsum.html

[6] United Nations Office on Drugs and Crime (2021) World Drug Report 2021. United Nations Publication.

[7] World Health Organisation (2023) Opioid Overdose. https://www.who.int/news-room/fact-sheets/detail/opioid-overdose

[8] United Nations Office on Drugs and Crime (2018) DRUG USE IN NIGERIA Executive Summary. United Nations Publication.

[9] Olanrewaju, J.A., Hamzat, E.O., Enya, J.I., Udekwu, M.O., Osuoya, Q., Bamidele, R.,

et al. (2022) An Assessment of Drug and Substance Abuse Prevalence: A Cross-Sectional Study among Undergraduates in Selected Southwestern Universities in Nigeria. *Journal of International Medical Research*, **50**, No. 10. https://doi.org/10.1177/03000605221130039

[10] Volkow, N.D. and McLellan, A.T. (2016) Opioid Abuse in Chronic Pain—Misconceptions and Mitigation Strategies. *The New England Journal of Medicine*, **374**, 1253-1263. https://doi.org/10.1056/NEJMra1507771

[11] Boscarino, J., Hoffma, S. and Han, J. (2015) Opioid-Use Disorder among Patients on Long-Term Opioid Therapy: Impact of Final DSM-5 Diagnostic Criteria on Prevalence and Correlates. *Substance Abuse and Rehabilitation*, **6**, 83-91. https://doi.org/10.2147/SAR.S85667

[12] Ballas, S.K. (2021) Opioids Are Not a Major Cause of Death of Patients with Sickle Cell Disease. *Annals of Hematology*, **100**, 1133-1138. https://doi.org/10.1007/s00277-021-04502-2

[13] Han, J., Zhou, J., Saraf, S.L., Gordeuk, V.R. and Calip, G.S. (2018) Characterization of Opioid Use in Sickle Cell Disease. *Pharmacoepidemiology and Drug Safety*, **27**, 479-486. https://doi.org/10.1002/pds.4291

[14] Ehrentraut, J.H., Kern, K.D., Long, S.A., An, A.Q., Faughnan, L.G. and Anghelescu, D.L. (2014) Opioid Misuse Behaviors in Adolescents and young Adults in a Hematology/Oncology Setting. *Journal of Pediatric Psychology*, **39**, 1149-1160. https://doi.org/10.1093/jpepsy/jsu072

[15] Uthman, K., James, B.O. and Omoaregba, J.O. (2022) Psychoactive Substance Use Disorders in an Adult Sickle Cell Disease Population in Nigeria: Prevalence and Correlates. *Journal of Substance Use*, **27**, 34-37. https://doi.org/10.1080/14659891.2021.1885516

[16] Bazuaye, G.N. and Uwadiae, E. (2016) Pentazocine Dependence among Sickle Cell Disease Patients Attending Outpatient Specialist Sickle Cell Clinic in Benin City, Nigeria. *Nigerian Journal of Psychiatry*, **14**, 25-29.

[17] Ernest, S.K., Kolawole, I.K., Olorunsola, B.O., Ogunkunle, O.T., Ojuola, O.A., Oyedepo, T.J., *et al*. (2019) Pentazocine Abuse in Two Siblings with Sickle Cell Anaemia. *Open Journal of Pediatrics*, **9**, 148-153. https://doi.org/10.4236/ojped.2019.92016

[18] Armiya'u, A.Y., Garba, B.I. and Haliru, D.G. (2016) Intravenous Pentazocine Dependence in a Young Sickle Cell Anemia Patient: A Case Report. *Edorium Journals*, **5**, 1-4. https://doi.org/10.5348/crint-2016-20-CR-1

[19] Kotila, T.R., Busari, O.E., Makanjuola, V. and Eyelade, O.R. (2015) Addiction or Pseudoaddiction in Sickle Cell Disease Patients: Time to Decide—A Case Series. *Annals of Ibadan Postgraduate Medicine*, **13**, 44-48.

[20] Fasipe, T.A. and Hulbert, M.L. (2022) Still Seeking Balance in Opioid Management for Acute Sickle Cell Disease Pain. *Pediatric Blood & Cancer*, **69**, e29741. https://doi.org/10.1002/pbc.29741

[21] Dhaliwal, A. and Gupta, M. (2022) Physiology, Opioid Receptor. StatPearls, Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK546642/

[22] Carroll, C.P. (2020) Opioid Treatment for Acute and Chronic Pain in Patients with Sickle Cell Disease. *Neuroscience Letters*, **714**, Article ID: 134534. https://doi.org/10.1016/j.neulet.2019.134534

[23] Levy, S.J., Williams, J.F. and AAP Committee on Substance Use and Prevention (2016) Substance Use Screening, Brief Intervention, and Referral to Treatment. *Pediatrics*, **138**, e20161211. https://doi.org/10.1542/peds.2016-1211

[24] Robinson, C.A. and Wilson, J.D. (2020) Management of Opioid Misuse and Opioid Use Disorders among Youth. *Pediatrics*, **145**, S153-S164. https://doi.org/10.1542/peds.2019-2056C

[25] Levy, S., Weiss, R., Sherritt, L., Ziemnik, R., Spalding, A., Van Hook, S., *et al.* (2014) An Electronic Screen for Triaging Adolescent Substance Use by Risk Levels. *JAMA Pediatrics*, **168**, 822-828. https://doi.org/10.1001/jamapediatrics.2014.774

[26] Kelly, S.M., Gryczynski, J., Mitchell, S.G., Kirk, A., O'Grady, K.E. and Schwartz, R.P. (2014) Validity of Brief Screening Instrument for Adolescent Tobacco, Alcohol, and Drug Use. *Pediatrics*, **133**, 819-826. https://doi.org/10.1542/peds.2013-2346

[27] American Psychiatric Association (2020) Table 3, DSM-5 Diagnostic Criteria for Diagnosing and Classifying Substance Use Disorders. Diagnostic and Statistical Manual of Mental Disorders.

[28] McGann, P.T., Nero, A.C. and Ware, R.E. (2013) Current Management of Sickle Cell Anemia. *Cold Spring Harbor Perspectives in Medicine*, **3**, a011817. https://doi.org/10.1101/cshperspect.a011817

[29] Charache, S., Terrin, M.L., Moore, R.D., Dover, G.J., Barton, F.B., Eckert, S.V., *et al.* (1995) Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. *The New England Journal of Medicine*, **332**, 1317-1322. https://doi.org/10.1056/NEJM199505183322001

[30] Wang, W.C., Ware, R.E., Miller, S.T., Iyer, R.V., Casella, J.F., Minniti, C.P., *et al.* (2011) Hydroxycarbamide in Very Young Children with Sickle-Cell Anaemia: A Multicentre, Randomised, Controlled Trial (BABY HUG). *The Lancet*, **377**, 1663-1672. https://doi.org/10.1016/S0140-6736(11)60355-3

[31] Ataga, K.I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., *et al.* (2017) Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *The New England Journal of Medicine*, **376**, 429-439. https://doi.org/10.1056/NEJMoa1611770

[32] Estepp, J.H., Kalpatthi, R., Woods, G., Trompeter, S., Liem, R.I., Sims, K., *et al.* (2022) Safety and Efficacy of Voxelotor in Pediatric Patients with Sickle Cell Disease Aged 4 to 11 Years. *Pediatric Blood & Cancer*, **69**, e29716. https://doi.org/10.1002/pbc.29716

[33] Yenamandra, A. and Marjoncu, D. (2020) Voxelotor: A Hemoglobin S Polymerization Inhibitor for the Treatment of Sickle Cell Disease. *Journal of the Advanced Practitioner in Oncology*, **11**, 873-877. https://doi.org/10.6004/jadpro.2020.11.8.7

[34] Eaton, W.A. and Bunn, H.F. (2017) Treating Sickle Cell Disease by Targeting HbS Polymerization. *Blood*, **129**, 2719-2726. https://doi.org/10.1182/blood-2017-02-765891

[35] Inoue, S., Khan, I., Mushtaq, R., Sanikommu, S.R., Mbeumo, C., LaChance, J., *et al.* (2016) Pain Management Trend of Vaso-Occulsive Crisis (VOC) at a Community Hospital Emergency Department (ED) for Patients with Sickle Cell Disease. *Annals of Hematology*, **95**, 221-225. https://doi.org/10.1007/s00277-015-2558-x

[36] Akinbami, A., Bola, O., Uche, E., Badiru, M., Olowoselu, O., Suleiman, A.M., *et al.* (2019) Pentazocine Addiction among Sickle Cell Disease Patients and Perception of Its Use among Health-Care Workers. *Journal of Applied Hematology*, **10**, 94-98. https://doi.org/10.4103/joah.joah_39_19

[37] Wilson, S.H., Hellman, K.M., James, D., Adler, A.C. and Chandrakantan, A. (2021) Mechanisms, Diagnosis, Prevention and Management of Perioperative Opioid-Induced Hyperalgesia. *Pain Management*, **11**, 405-417. https://doi.org/10.2217/pmt-2020-0105

[38] Al Zahrani, O., Hanafy, E., Mukhtar, O., Sanad, A. and Yassin, W. (2020) Outcomes of Multidisciplinary Team Interventions in the Management of Sickle Cell Disease Patients with Opioid Use Disorders: A Retrospective Cohort Study. *Saudi Medical Journal*, **41**, 1104-1110. https://doi.org/10.15537/smj.2020.10.25386

[39] Ajayi, T.A., Edmonds, K.P., Thornberry, K. and Atayee, R.A. (2016) Palliative Care Teams as Advocates for Adults with Sickle Cell Disease. *Journal of Palliative Medicine*, **19**, 195-201. https://doi.org/10.1089/jpm.2015.0268

[40] Karsenty, C., Tubman, V.N., Liu, C.J., Fasipe, T. and Wyatt, K.E. (2022) Regional Anesthesia for Sickle Cell Disease Vaso-Occlusive Crisis: A Single-Center Case Series. *Pediatric Blood & Cancer*, **69**, e29695. https://doi.org/10.1002/pbc.29695