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Systematic review

Patterns of Opioid Utilization and Aberrant Opioid-Related Behaviors (AORB) in Pediatric Sickle Cell Anemia Patients: A Systematic Review

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Abstract

Background: Sickle cell disease (SCD) causes recurrent vaso-occlusive pain in childhood which requires opioid analgesia. Opioid utilization and aberrant opioid-related behaviors (AORB) still poorly defined in pediatric Gulf Cooperation Council (GCC) populations. **Objective:** This systematic review analyzed data on opioid utilization patterns, AORB, opioid use disorder (OUD), and related psychosocial factors in pediatric patients with SCD. **Methods:** Searches were conducted in PubMed, Web of Science, Scopus, and Embase using terms related to SCD, opioid analgesics, AORB, and pediatric. We consider original cohort, cross-sectional, retrospective, and qualitative studies involving pediatric SCD populations and reporting opioid utilization or AORB. We extract data on study setting, population, opioid-related outcomes, and main findings. **Results:** Seven studies were included. GCC studies was limited to one Saudi tertiary emergency department study, where morphine was used commonly for acute painful crises and administration within 60 -

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minutes was associated with higher chance of discharge. International claims data showed that 40% of SCD patients used opioids annually, while 3% of pediatric patients were high-dose users. OUD prevalence in adolescents with SCD was reported as 5.3% in Uganda. Additional opioid use was associated with older age, previous healthcare utilization, depression, pain catastrophizing, caregiver factors, and family support. **Conclusion:** Opioid utilization in pediatric SCD is affected by recurrent vaso-occlusive pain and acute care needs, data on AORB in GCC children are very limited.

Keywords

Sickle cell disease; sickle cell anemia; pediatric; opioids; opioid utilization; aberrant opioid-related behaviors

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder characterized by abnormal hemoglobin S polymerization, red-cell sickling, hemolysis, vaso-occlusion, and multisystem complications that begin early in childhood (Egesa 2022). In Saudi Arabia and other Gulf Cooperation Council (GCC) countries, SCD is an important public health problem because of its regional clustering, inherited transmission, and continuing burden of painful crises and hospital use (Jastaniah 2011). Saudi data show geographic variation in SCD prevalence, and higher frequencies reported in the Eastern and Southwestern regions, while recent Saudi reviews describe vaso-occlusive crises, acute chest syndrome, infections, anemia, and pain attacks as common complications (Jastaniah 2011; Hamed 2024).

Pain is one of the most important manifestations of SCD and is a major reason for ED visits and hospitalization in children (Zempsy 2010). In Saudi pediatric cohorts, acute painful crisis reported as a leading cause of hospitalization, and ED studies show that children with SCD commonly present with pain and fever (Abd Elmoneim 2019; Almahmoud 2023). Because vaso-occlusive pain can be severe and recurrent, clinical guidelines show rapid assessment, timely analgesia, individualized

opioid dosing when opioids are indicated, and frequent reassessment in acute care settings (Brandow 2020). In a Saudi tertiary ED study, morphine was commonly used for acute painful crises, and earlier analgesic administration was associated with a higher rate of discharge from the ED (Almahmoud 2023).

Opioids are central to the treatment of moderate to severe SCD pain, and their use requires careful interpretation because analgesic need coexist with concerns about tolerance, dependence, adverse effects, stigma, and misuse (Phillips 2023). Large claims-based data indicate that opioid exposure in SCD is variable, with many patients receiving low doses and a minority of pediatric patients receiving high daily oral morphine-equivalent doses (Han 2018). Recent data in opioid-naïve children with SCD did not identify a concerning pattern of progressive long-term opioid escalation during three years after the first prescription (Snyder 2024). These findings indicate that opioid utilization should be studied in relation to pain severity, healthcare use, and disease burden rather than assumed to represent aberrant behavior (Snyder 2024).

Home opioid use is important because many SCD pain episodes are managed outside hospital settings (Valrie 2024). Pediatric studies found that home

opioid use is associated with pain severity, age, positive affect, negative affect, and caregiver catastrophizing (Stone 2020; Valrie 2024). A qualitative study found that families make opioid decisions through a complex process involving perceived benefits, side effects, previous healthcare experiences, provider communication, and fear of stigma (Phillips 2023).

Aberrant opioid-related behaviors (AORB) and opioid use disorder (OUD) is under-studied in pediatric SCD in GCC populations. An adolescent Ugandan study found OUD prevalence of 5.3%, with depression increasing risk and living with family showing a protective association (Kwagala 2024). In Oman, an adult SCD study reported a high risk of AORB and identified lack of family support as an associated factor (Al Abulsalam 2025). Our systematic review aims to analyze original articles on opioid utilization and AORB in pediatric SCD, with attention to GCC data and the major gaps requiring attention.

Methods

The methodology for this systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a transparent synthesis of the literature regarding opioid utilization and AORB in pediatric SCD.

Search strategy

A systematic search was performed in four major electronic databases: PubMed, Web of Science (WoS), Scopus, and Embase. The search strategy used a combination of Medical Subject Headings (MeSH) terms and keywords related to "Sickle Cell Anemia," "Opioid Analgesics," "Aberrant Opioid-Related Behaviors," "Pediatrics," and "Gulf

Cooperation Council" countries (including Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Oman, and Bahrain). The search string was adapted for each database using Boolean operators (AND/OR). The PubMed search included terms: ("Anemia, Sickle Cell" [MeSH]) AND ("Analgesics, Opioid" [MeSH] OR "Opioid-Related Disorders" [MeSH]) AND ("Child" [MeSH] OR "Adolescent" [MeSH]).

Eligibility criteria

Studies were included if they focused on pediatric populations (ages 0–19 years) diagnosed with SCD; reported on patterns of opioid utilization (dosage, frequency, type) or identified aberrant behaviors (addiction, misuse, non-adherence, Opioid Use Disorder); and were original research articles (cohort, cross-sectional, retrospective, or qualitative). While the primary focus was on the GCC region, international studies were screened to provide a global benchmark for AORB prevalence in pediatric SCD. We exclude case reports, editorials, or focused on adult populations.

Study selection and data extraction

Title and abstract screening were performed by reviewers, followed by a full-text review of eligible articles. Discrepancies resolved through consultation with a third reviewer. Data extraction performed using a standardized template, capturing information on the first author, year of publication, study design, country, population characteristics, inclusion criteria, specific AORB, and primary findings.

Quality assessment

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies (cohort and cross-

sectional) and the Critical Appraisal Skills Programme (CASP) or JBI Critical Appraisal Tool for qualitative and case series designs (Table 1). The NOS evaluates three domains: Selection of participants, Comparability of groups, and

Outcome/Exposure assessment. A maximum of 9 stars can be awarded, with scores ≥ 7 generally considered "High Quality," 5–6 "Fair Quality," and < 5 "Poor Quality."

Table 1: Quality assessment of the included studies

Citation	Study design	Appraisal tool	Selection (Max 4*)	Comparability (Max 2*)	Outcome (Max 3*)	Total score / quality level
Snyder et al., 2024	Retrospective Cohort	NOS	****	*	***	8/9 (High)
Han et al., 2017	Retrospective Cohort	NOS	****	*	***	8/9 (High)
Almahmoud et al., 2023	Retrospective Study	NOS	***	*	***	7/9 (High)
Kwagala et al., 2024	Cross-sectional	NOS (Modified)	***	*	**	6/9 (Fair)
Stone et al., 2020	Prospective Diary	NOS	***	*	**	6/9 (Fair)
Phillips et al., 2023	Qualitative Study	CASP				High Quality*
Buchheit et al., 2020	Case Series	JBI				Moderate Quality**

Results

The systematic review found a different range of articles studied opioid use in pediatric SCD, and data specific to the GCC region is limited compared to North American and African cohorts. The results are categorized into utilization patterns, prevalence of aberrant behaviors, and psychological correlates.

Opioid utilization patterns in the GCC and globally

Data from Saudi Arabia indicates a heavy reliance on morphine for managing acute painful crises in tertiary pediatric settings. One retrospective study

found that morphine was utilized in 84.4% of ED episodes. A critical finding was the impact of timing; administration within 60 minutes of presentation improved the likelihood of discharge from the ED. Internationally, national claims data show that 40% of pediatric SCD patients utilize opioids annually. While the majority are maintained on low-dose regimens, 3% of pediatric patients transition to high-dose utilization (defined as >30 mg Oral Morphine Equivalents daily).

Prevalence and patterns of AORB and OUD

The prevalence of OUD among adolescents with SCD differ geographically. In sub-Saharan African cohorts, the prevalence was 5.3%. In North American cohorts, longitudinal data 14% of opioid-naive children fill a second prescription within three years of their initial exposure. Older age and higher frequency of healthcare utilization were predictors of potentially prolonged opioid use. Caregivers and patients describe a complex decision-making process for home opioid use, where the fear of side effects and stigma competes with the necessity of managing debilitating pain.

Psychological and social correlates

Aberrant behaviors and utilization patterns were linked to psychological factors. High levels of pain catastrophizing in youth and their caregivers were

associated with an increased probability of home opioid use. Depression was identified as a major risk factor for OUD, with higher depression scores correlating with increased odds of disorder. Protective factors including living with family were identified.

Emerging management strategies

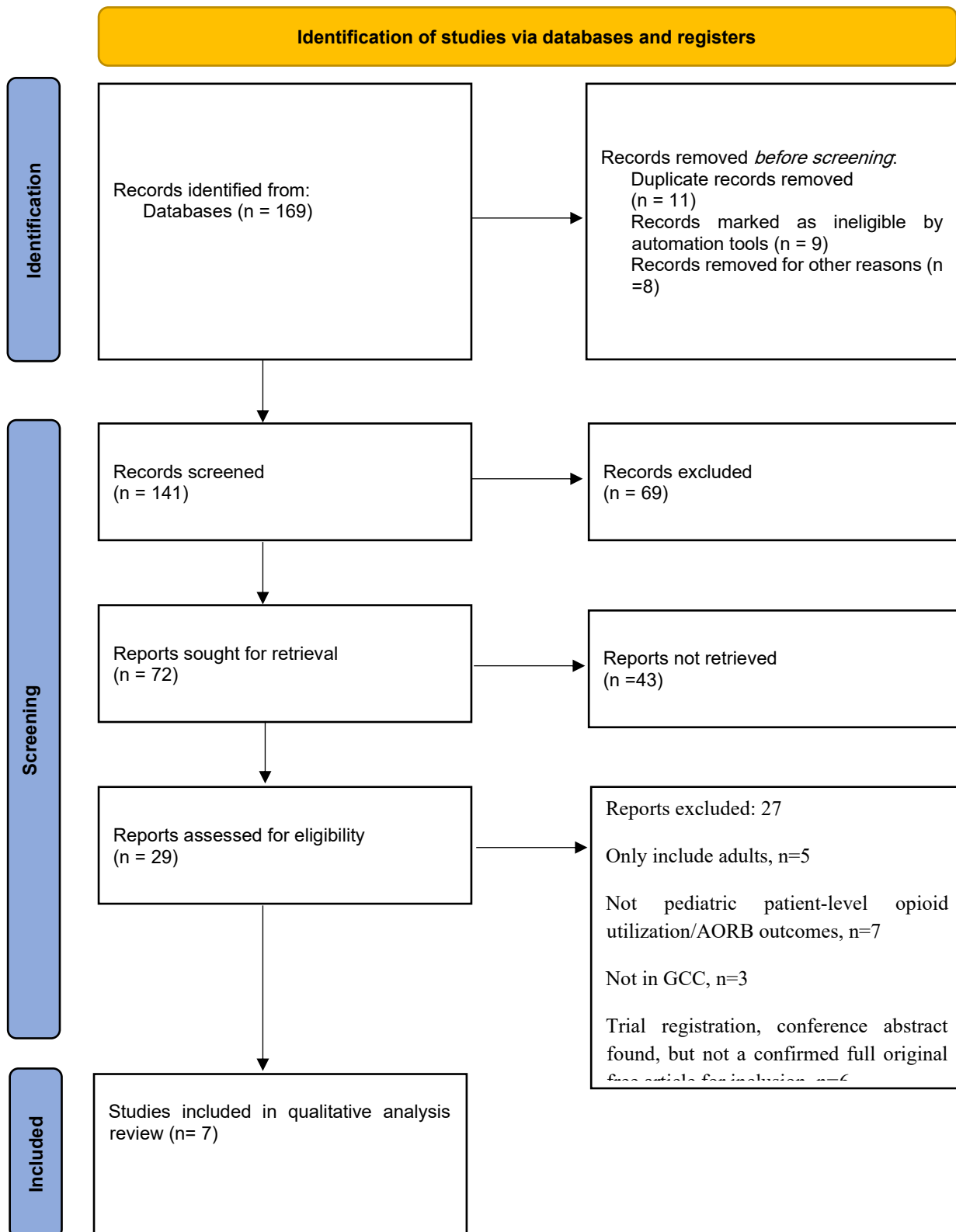
For patients identified with complex opioid needs or AORB, emerging evidence supports the feasibility of Medication for Opioid Use Disorder. Case series data indicate that ambulatory microdose induction of buprenorphine-naloxone is a safe and effective method for stabilizing pain management in adolescents with SCD who exhibit signs of complex dependence or refractory pain. Characteristics of the included studies presented in (Table 2).

Table 2: characteristics of the included studies

Citation	Study design	Country and setting	Population	Inclusion criteria	AORB	Main findings and outcomes
Kwagala et al., 2024	Cross-sectional Study	Uganda; Tertiary Hospital (Mulago Hospital)	Adolescents with SCD (n=356)	Adolescents aged 10–19 years with confirmed SCD	OUD prevalence and associated factors	The prevalence of OUD was 5.3%. Significant risk factors included higher depression scores, while living with family was a protective factor.
Snyder et al., 2024	Retrospective Cohort Study	USA; Medicaid Claims (Georgia)	Opioid-naive children with SCD (n=2,565)	Aged 1 to 15 years with SCD; filled ≥ 1 opioid prescription after 1 year without use	Patterns of opioid use and additional opioid use within 3 years of first prescription.	Among children who filled an initial prescription, 14% filled a second prescription within 3 years. Older age and previous healthcare use were linked to subsequent use.
Han et al., 2017	Retrospective Cohort Study	USA; National Claims Database	SCD patients (n=3,882)	SCD diagnosis in medical claims; continuous	Patterns of utilization, including	40% of patients used opioids annually. While most pediatric patients used low doses, 3% of pediatric patients were

Citation	Study design	Country and setting	Population	Inclusion criteria	AORB	Main findings and outcomes
				12-month enrollment	prevalence and dosage (OME).	identified as high-dose users (>30 mg OME daily).
Phillips et al., 2023	Qualitative Study	USA; Multi-center	Caregivers (n=20) and patients with SCD	Caregivers of children with SCD and patients involved in home opioid decision-making	Decision-making processes for home opioid use and perceived risks and benefits.	Decision-making is influenced by multilevel stressors and patient-provider interactions. Families balance side effect risks with the need for pain relief.
Stone et al., 2020	Prospective Daily Diary Study	USA; Outpatient Hematology Clinic	Children with SCD (n=32) and caregivers (n=28)	Pediatric with SCD and their primary caregivers	Associations between psychological factors and home opioid use	Youth and parent catastrophizing were significantly associated with an increased likelihood of using opioids at home.
Buchheit et al., 2020	Case Series	USA; Academic Medical Center (OHSU)	Two adolescent patients with SCD	Adolescents with SCD and complex pain and opioid management needs	Microdose induction of buprenorphine-naloxone	Ambulatory microdose induction of buprenorphine-naloxone was feasible and safe for managing SCD patients with complex opioid needs.
Almahmoud et al., 2023	Retrospective Study	Saudi Arabia (GCC); Tertiary Hospital (King Abdullah Specialist Children's Hospital)	Children with SCD (n=291 episodes)	Pediatric patients with SCD presenting to the ED with fever or acute painful crises	Management of acute painful crises and timing of opioid administration in the ED	Morphine was the most common opioid used (84.4%). Timely administration (within 60 mins) was associated with a higher rate of discharge from the ED.

Fig 1: PRISMA flow chart



Discussion

The present review shows that opioid use in pediatric SCD is linked to the clinical burden of vaso-occlusive pain rather than being interpreted as aberrant behavior (Han 2018). In the Saudi context, painful crises is a major reason for acute care use, as one Saudi pediatric study reported acute painful crisis as the leading cause of hospitalization, while another tertiary ED study found pain crisis to be the most common presentation in children with SCD (Abd Elmoneim 2019; Almahmoud 2023). This supports the importance of timely analgesia in ED, especially because the Saudi ED study reported frequent use of morphine and showed that earlier analgesic administration was associated with better ED outcomes (Almahmoud 2023).

In a large study, 40% of patients used opioids during a 12-month period, and most pediatric patients received low daily oral morphine equivalent doses (Han 2018). High opioid exposure is concentrated in a limited subgroup with more severe disease complications and higher healthcare utilization (Han 2018). The study of opioid-naive children showed no clear pattern of progressive long-term opioid escalation after the first prescription, although greater vaso-occlusive crisis burden was associated with longer opioid supply (Snyder 2024).

The findings highlight the importance of home opioid use, because many pain episodes are managed outside hospital settings (Zempsky 2010). Ecological assessment data showed that a proportion of youth used opioids during the observation period, and opioid use was related to pain severity, older age, and lower positive affect (Valrie 2024). These results indicate that pediatric opioid use is affected by pain intensity and psychosocial context, which is consistent with the

biopsychosocial model of sickle cell pain management (Brandow 2018). AORB should be interpreted with pain frequency, functional impairment, emotional state, family support, and previous healthcare experiences (Brandow 2018).

Decision-making about opioids is complex for children, caregivers, and providers (Phillips 2023). Families balance the need for pain relief against concerns about side effects, tolerance, dependence, stigma, school disruption, and avoiding emergency department visits (Phillips 2023). This is relevant to AORB assessment because concerning behaviors reflect fear, undertreated pain, poor access to timely care, or previous negative encounters with healthcare providers (Zempsky 2010). Catastrophizing, depression, and emotional factors are associated with opioid use or opioid-related disorder supports the need for psychological screening in pediatric sickle cell care (Stone 2020; Kwagala 2024).

Literature shows a major regional gap (Arzoun 2022), although Saudi studies describe ED and hospitalization patterns, direct GCC data on pediatric opioid utilization, AORB, misuse, or OUD is very limited. Most studies on opioid patterns and psychosocial correlates comes from non-GCC settings, limiting generalizability to Gulf populations with different healthcare systems, prescribing practices, family structures, and sickle cell genotypes (Han 2018; Snyder 2024). Future GCC studies should use standardized definitions of opioid utilization, AORB, OUD, pain severity, and psychosocial risk factors to distinguish appropriate analgesic use from problematic AORB.

Conclusion

This review indicates that opioid utilization in pediatric SCD is driven by recurrent vaso-occlusive pain and acute care needs, data on AORB in GCC children are very limited. The only GCC pediatric study identified was from Saudi Arabia and focused on ED rather than misuse or long-term opioid behavior. International studies indicate that most pediatric opioid use is low dose, while high-risk use is concentrated in smaller subgroups linked to pain burden, healthcare utilization, depression, catastrophizing, and family support. Future GCC studies should use standardized pediatric definitions for opioid use, AORB, OUD, and clinical outcomes in settings.

List of abbreviations

AORB, Aberrant opioid-related behaviors

CASP, Critical Appraisal Skills Programme

ED, Emergency department

GCC, Gulf Cooperation Council

JBI, Joanna Briggs Institute

MeSH, Medical Subject Headings

NOS, Newcastle-Ottawa Scale

OME, Oral morphine equivalents

OUD, Opioid use disorder

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SCD, Sickle cell disease

USA, United States of America

WoS, Web of Science.

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