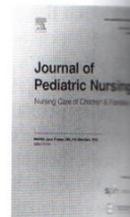




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Non-pharmacological pain interventions for sickle cell crisis in pediatrics: A scoping review



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ABSTRACT

Problem: Sickle cell crises (SCC) are recurrent, severe pain episodes experienced by people living with sickle cell disease (SCD). Non-pharmacological interventions have been recommended for SCC pain management however, little is known about the impact of these interventions on SCC pain. This scoping review aims to systematically identify evidence on the use and effectiveness of non-pharmacological interventions for pain management during SCC in the pediatric population.

Eligibility criteria: Studies were eligible if they are published in English and focusing on the use of any non-pharmacological interventions on pain during SCC in pediatric patients. Nine databases were searched including Medline, CINAHL and PsychInfo. Also, the reference lists of relevant studies were searched.

Sample: The database searching yielded 1517 studies. After the title and abstract screening, 1348 studies were excluded, and 169 full texts were retrieved and screened. One study was identified through handsearching. Finally, 27 articles were included in this scoping review.

Results: Across all studies, 27 different non-pharmacological interventions were identified. There were inconsistent results regarding the effectiveness of virtual reality, guided imagery, and cognitive-behavioral interventions in experimental studies. The most common interventions used at home were prayer, massage, and distraction. The main interventions used in hospitals were prayer and fluid intake, but this was explored by a few studies.

Conclusion: Pediatric SCD patients use numerous non-pharmacological interventions to manage pain during SCC. However, the impact of many interventions on SCC pain has not been empirically investigated.

Implications: Further research is necessary to establish the effectiveness of non-pharmacological interventions on SCC pain.

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Introduction

Sickle-cell disease (SCD) refers to a group of inherited disorders caused by mutations in the β -globin gene (Piel et al., 2017). These disorders are characterized by the propensity of red blood cells to transform into sickle (or crescent) shapes (Ware et al., 2017). Of these disorders, the most common and severe form is sickle-cell anemia (SCA), which is the homozygosity of the β^S allele. It affects the black population of African descent at much higher rates than people of other ethnicities and is theorized to have evolved in human populations living where malaria is common to help protect against the disease (Rees et al., 2010; Ware et al., 2017).

Approximately 300,000 infants are diagnosed with SCA annually, and 57% of these newborns are in Nigeria, the Democratic Republic of Congo, and India (Piel et al., 2013). According to a 2020 report, the global incidence for all types of SCD was 610,000 cases per year in 2017 and there was approximately 3.14 million people living with SCD globally (Lippi & Mattiuzzi, 2020). Moreover, SCD accounted for the highest cause-specific disability-adjusted life years (3.05 million) compared to other inherited erythrocyte disorders such as G6PD Deficiency and thalassemia, and it accounted for 38,420 deaths in 2017. SCD had a peak of prevalence in 69% of all cases between the ages of 0 to 15 years, with 57% of all deaths occurring in this age group (Lippi & Mattiuzzi, 2020). >75% of the global burden of SCD is in sub-Saharan Africa, where scarce resources, topical infections like malaria, and inadequate awareness among healthcare professionals contribute to high mortality rates in children under the age of 5 years old living with SCD (McGann et al., 2017; Piel et al., 2013). In Africa, the under-5 mortality

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in this particular population is 50%–90% (Grosse et al., 2011). <5% of newborns (approximately 13,000) with SCA are born in North America and Europe (Piel et al., 2013). However, it is the most common inherited blood disease in the US (Sedrak & Kondamudi, 2021).

The leading cause of hospitalization for young people with SCD is sickle cell crisis (SCC) (Hejazi et al., 2021). This crisis is characterized by recurrent and unpredictable episodes of acute moderate to severe pain, lasting for an average of seven days (National Health Service, 2019). On average, patients with SCD experience at least one severe episode every year (National Health Service, 2019). Patients with SCD have described the pain as immeasurable and unbearable (Coleman et al., 2016). This crisis can lead to fatal consequences such as multi-organ failure, sudden death, and acute chest syndrome (Coleman et al., 2016). For pediatric patients with SCD, these painful episodes can lead to depression, diminished quality of life, limited participation in social activities, and hindered academic progress (Adeyemo et al., 2015; Jonassaint et al., 2016; Pandarakutty et al., 2020).

The first line of treatment for SCC pain is pharmacological interventions such as opioids and non-opioids (for example acetaminophen and non-steroidal anti-inflammatory drugs) (Uwaezuoke et al., 2018). However, when used alone, medications do not provide optimal relief for pain and the associated psychosocial implications of severe acute pain such as stress, fear, and anxiety (Uwaezuoke et al., 2018). This can lead to adverse effects such as depression. Poorly managed SCC pain can lead to patients requesting more analgesia which has been shown to contribute to the stigmatization and labeling of patients with SCD as exhibiting drug-seeking behaviors by healthcare professionals (Stewart et al., 2021). Patients with SCD continue to complain that their pain is often misunderstood and undertreated (Coleman et al., 2016; Darbari et al., 2020; Hejazi et al., 2021; Sagi et al., 2021). Hence, experts have recommended that pharmacological interventions should be used in conjunction with non-pharmacological interventions (NPIs) to improve the pain experiences of patients with SCD during crises (Brandow et al., 2020; National Heart Lung and Blood Institute, 2014).

NPIs (sometimes referred to as adjunctive or complementary interventions) have the potential to help relieve pain, reduce analgesic use, improve patients' experience with pain and reduce the length of hospitalization in children with SCD. Expert panels have recommended heat application, distraction, massage, yoga, transcutaneous electrical nerve stimulation, virtual reality, and guided audio-visual relaxation for managing SCC pain (Brandow et al., 2020; National Heart Lung and Blood Institute, 2014). These interventions use various mechanisms to reduce SCC pain, for instance, heat application might improve SCC pain by dilating blood vessels and improving circulation which contributes to resolving the vaso-occlusion occurring in SCC. Also, virtual reality might improve SCC pain by immersing the patient in a virtual environment hence distracting the patient's attention from pain (Fuchs & Guitton, 2019). The effectiveness and efficacy of NPIs on acute pain have been established in pediatric patient populations such as burns, cancer, and procedural pain (Bukola & Paula, 2017; Hadoush et al., 2021; Woragidpoonpol et al., 2013).

For pediatric patients with SCD, various narrative reviews recommended different NPIs for SCC pain but with limited evidence (Amid & Odame, 2014; Lakkakula et al., 2018; Telfer & Kaya, 2017; Zempsky, 2010). It is unclear if these reviews involved a systematic search of the literature on the use of NPIs for SCC pain, as their main focus was on SCD pain management in general. Also, the types of NPIs used by children and their caregivers to manage their SCC pain remain unclear. Therefore, this scoping review aimed to provide an overview of the evidence on the forms of NPIs used for SCC pain in pediatric patients. The focus is on SCC pain, and not chronic pain in SCD as there is a great deal of literature on the use of NPIs for managing chronic pain in pediatric patients whereas, there appears to be no scoping or systematic reviews specifically focused on SCC pain. This review highlights the research gaps in this field and the existing disparities in the use of NPIs at home and the hospital, and across regions worldwide.

Methodology

A scoping review was conducted to systematically identify available evidence on the use of NPIs for the management of SCC pain in the pediatric population, determine and analyze the gaps of knowledge in this field, and present recommendations for future research. Prior to undertaking this review, the Cochrane Library of Systematic Reviews and Prospero were searched to ensure a similar review had not been conducted. No prior scoping or systematic review was identified. This scoping review was guided by the methodological framework suggested by Arksey and O'Malley (2005) and the Joana Briggs Institute (JBI) guidelines for conducting scoping reviews (Peters et al., 2020). Arksey & O'Malley's approach consists of five stages: 1) identifying the research questions, 2) identifying relevant studies, 3) study selection, 4) charting the data, and 5) collating, summarizing, and reporting the results (Arksey & O'Malley, 2005). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) was used to guide the reporting of the review.

Study identification

A preliminary search was conducted in Medline, Embase, Cumulated Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar to identify relevant studies that helped identify suitable keywords. The Yale Mesh Analyzer was also used to identify relevant keywords. With the guidance of a specialized librarian, the search strategies were developed for eight databases: Medline, Embase, Cochrane Library of Systematic Reviews, JBI EBP Database, Cochrane Central Register of Controlled Trials, CINAHL, PsychInfo, and Proquest. The search strategies entailed subject headings and keywords, using appropriate truncations for each database, and describing the patient population, the disease, and the intervention. Examples of keywords describing the patient population include "child" and "adolescent." Examples of keywords describing the disease include: "sickle cell crisis" and "vaso-occlusive crisis." Examples of keywords describing the intervention include: "music", "virtual reality" and "cognitive behavioral therapy." A sample of the search strategy is in the Supplementary material. There were no date limitations; the search was from the inception of the database to February 23, 2022. There was no restriction to location but limited to reports published in English. Finally, reference lists of key articles were searched to identify additional relevant studies.

Study selection

The Covidence systematic review management software (Covidence, 2021) was used to facilitate the study selection process. Studies were selected based on the inclusion and exclusion criteria (Table 1). The age limit was extended to 21 years to accommodate studies from countries where the pediatric age range was up to 21. The selection process was conducted by one author (BMI). The studies identified from the various databases were imported into Covidence;

Table 1
Selection criteria.

	Inclusion criteria	Exclusion criteria
1	Studies of any design	Studies on pediatric patients with SCD and other patient populations that did not present the findings of pediatric patients with SCD separately
2	Included pediatric patients (0–21 years) experiencing sickle cell crisis	Focused on chronic pain and other SCD pain syndromes
3	Included any form of non-pharmacological interventions	
4	Focused on pain during sickle cell crisis	

duplicates were automatically removed by the software. The titles and abstracts were screened, and irrelevant studies were removed. After the screening process, the full texts of the remaining studies were retrieved and screened against the inclusion and exclusion criteria. Studies that met the selection criteria were included in the review.

Data extraction

A data extraction template was developed in Covidence (Covidence, 2021) which was designed to extract: the authors' details, year of publication, country, study design, inclusion and exclusion criteria guiding participants' selection, study objectives, number of participants, age and sickle cell status of the participants, the intervention, who administered the intervention, where and how often the intervention was used, the side-effects of the intervention, the pain assessment tools and other measures used, the study results, and limitations.

Data synthesis

The extracted data were imported into Excel and were analyzed quantitatively using descriptive statistics (frequencies were calculated as percentages) and narratively summarized. For cross-sectional studies exploring the types of NPI used at home, the frequencies of the responses for each NPI were summed across the studies. Some studies were excluded from this analysis because their analyses were based on narrative daily pain diary entries instead of standardized study measures. As there were a large number of NPIs and different methodologies used in the identified studies, classifying them into three logical categories was undertaken to clarify reporting of the results. The papers were categorized based upon research methodology (experimental versus non-experimental), location of interventions use (hospital versus home), and based upon a previously established taxonomy. The NPIs identified in this review were categorized by two major groupings: biomedical or alternative health NPIs. Biomedical NPIs are defined as interventions developed from the application of biomedical science, based on the principles of biology, physics, and biochemistry, to healthcare research or practice (Garrett et al., 2021). Biomedical NPIs were further classified into physical manipulative interventions, physical exercise, distraction, and other biomedical NPIs.

Alternative health interventions are defined as those practices that largely originated from traditions and theories distinct from contemporary biomedical science, and which claim mechanisms of action outside of those currently accepted by scientific and biomedical consensus (Garrett et al., 2021). The alternative health interventions were classified further under alternative health belief systems, herbal and nutritional interventions, and mind-body interventions. The 'other biomedical NPIs' group included interventions that did not fit into any of the respective sub-categories. In this review, a third category, "combined interventions", was created for interventions that used a combination of two or more biomedical NPIs and alternative health interventions, for instance: cognitive behavioral interventions with multiple components such as guided imagery, distraction techniques and breathing exercises.

No inferential statistical analyses and critical appraisal of the studies were performed as the aim of this scoping review was to describe the types of NPI used for the management of SCC. It was noted that various synonyms of the same words were used across the studies; hence, to achieve consistency in this paper, one word was adopted for each intervention to replace all suitable variations across the studies. For instance: heat application is referred to as heat or heat pad, and massage is referred to as rubbing.

Results

The database searches yielded 1517 studies, and after duplicates were removed, 1136 studies remained (Fig. 1). The titles and abstracts

of the remaining studies were screened, and 953 studies were deemed irrelevant based on the inclusion and exclusion criteria as they were focused on areas such as cancer care and HIV. The full texts of the remaining 183 studies were screened against the inclusion and exclusion criteria. The full texts of 11 studies (very old papers:1980–1993), could not be retrieved and were excluded. After screening a total of 143 studies were omitted for various reasons, such as studies that did not focus on NPIs or focused on chronic pain in SCD. One study was identified through handsearching. Finally, a total of 27 articles were included in this scoping review. One of the included studies is a quasi-experimental study on the use of video games that included only two children with SCC and did not separate the findings for the two children; also, the authors collected data on the use of NPIs for SCC management using a demographic questionnaire (Ali, 2014). Therefore, the data from the RCT part of that study were excluded because they did not meet the selection criteria, but the survey data were included in this review.

Characteristics of the studies

The majority of studies ($n = 23, 85\%$), were conducted in the United States (Fig. 2). Three studies were conducted in LMICs (Campelo et al., 2018; Oshikoya et al., 2015; Schmidt, 2008). The total sample of all included studies is 828 participants. Of this number, 126 participants were parents/caregivers of children and adolescents living with SCD from three studies (Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006), and 23 participants were healthcare professionals caring for pediatric patients with SCD in two other studies (Campelo et al., 2018; Neri et al., 2016). The majority of papers reported experimental work ($n = 15, 56\%$). Most studies (63%) were conducted between 2011 and 2021. See Table 2 for the characteristics of the included studies and Fig. 3 for the number of papers published per decade.

Categorization of NPIs

A total of 27 different NPIs were identified across all the included studies. The largest category of NPIs was biomedical NPIs with 18 different interventions. Table 3 shows the categorization of all the NPIs identified in this review. Based on patients' reports from four studies ($n = 312$), biomedical NPIs were the most used (69%, $n = 215$) (Ali, 2014; Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006). For all sub-categories, the most used interventions were physical manipulative interventions (32%, $n = 99$), followed by alternative health belief systems (27%, $n = 84$). Under biomedical NPIs, the most common was distraction (11.1%, $n = 35$). Figs. 4 and 5 show the frequencies of use of alternative health interventions and biomedical NPIs respectively. For the 'combined interventions' category, there was only one participant who chose yoga as an NPI they used at home.

Types of studies

Experimental studies

Seven randomised controlled trials and eight quasi-experimental studies were identified that explored the effect of various NPIs on pain during SCC. All these studies were conducted in the United States and included a total of 317 participants ranging from age 4 to 21 years. Seven studies found yoga, biofeedback-assisted relaxation, acupuncture, virtual reality, guided imagery, and cognitive-behavioral intervention with multiple components to be significantly effective in reducing SCC pain in pediatric patients with SCD (Agrawal et al., 2019; Cozzi et al., 1987; Dobson, 2006; Hood et al., 2021; Moody et al., 2017; Reece-Stremtan et al., 2021; Schatz et al., 2015). In contrast, four studies found that music, virtual reality, guided imagery and cognitive-behavioral intervention with multiple components did not result in a statistically significant reduction in SCC pain (Barakat et al., 2010; Braniecki, 2003; Chiami, 2015; Diaz-Hennessey et al., 2019).

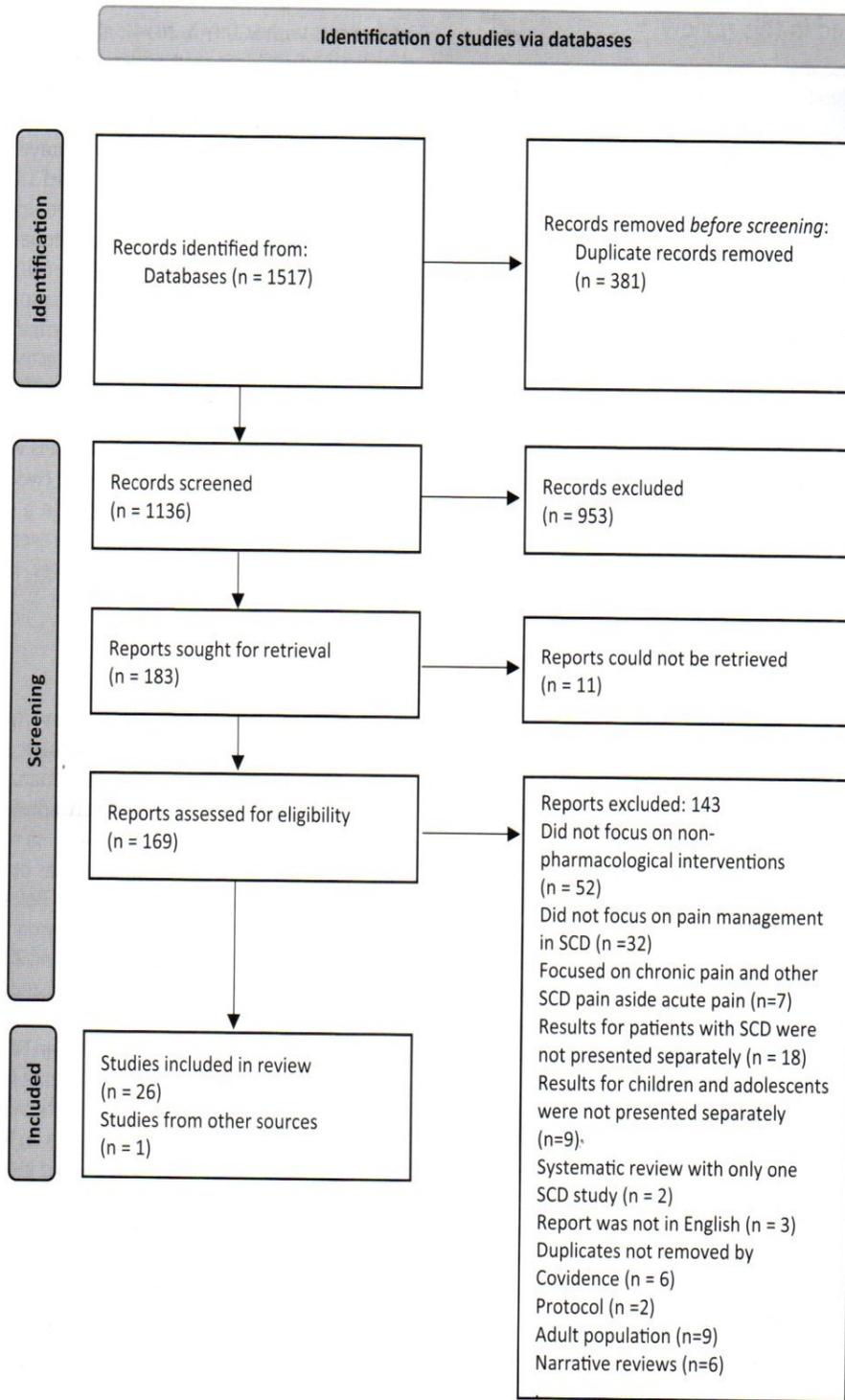


Fig. 1. PRISMA Flow diagram. The figure depicts the process of selecting the studies included in this scoping review.

Four studies did not determine the statistical significance for pain outcomes; instead, they described the impact of the intervention on the pain and other related outcomes (Bhushan et al., 2015; Schwartz et al., 2007; Sil et al., 2021; Wihak et al., 2020). In a quasi-experimental study of two patients, Bhushan et al. (2015) reported that acupuncture resulted in some pain reduction in patients, and it was acceptable to both participants. Schwartz et al. (2007) developed a home-based pain intervention that was deemed acceptable by the participants, but its impact on pain outcomes was not stated. Sil et al. (2021) reported that an educational intervention on cognitive-behavioral therapies improved patients' knowledge of SCC pain management, though its impact on the pain was not assessed. Wihak et al. (2020) pilot-tested a video-based cognitive-behavioral intervention for SCC pain and they reported that the intervention was well-

accepted by the children and adolescents with SCD, and it was feasible to use in both inpatient and out-patient departments. Finally, a wide range of pain measures was used across these studies, and the most common were pain diaries (n = 3) and the Wong-Baker FACES scale (n = 2).

Non-experimental studies

There were twelve studies that explored the use of NPIs for SCC pain in pediatrics, both in hospitals and at home. Using various non-experimental methods, these studies explored the types of interventions used by pediatric patients with SCD at home and in hospitals, the patients' views on various NPIs, and healthcare professionals' perspectives on NPIs for the management of SCC pain. Most studies were qualitative (33%); other methodologies include cross-sectional (25%)

Countries represented in this review

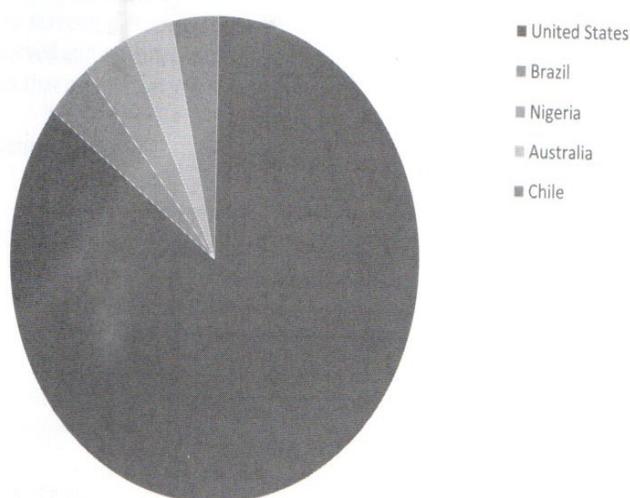


Fig. 2. Origin of the studies.

This figure shows the countries where the included studies were conducted.

and longitudinal studies (25%), retrospective chart review (8.3%), and case report (8.3%).

Research context

Interventions in hospitals

Six studies, (one retrospective, one longitudinal, one case report, and three qualitative studies), identified various NPIs used in hospital settings (Table 2). One US-based retrospective chart review reported that acupuncture was used in their hospital, and it effectively reduced pain during SCC with no adverse effects (Tsai et al., 2020). A longitudinal study conducted in Nigeria also reported that fluid intake and prayer were the only NPIs used during emergency admission for SCC (Oshikoya et al., 2015). This was the only study found conducted in Africa. Another case report described how guided imagery reduced the pain caused by SCC in a 10-year-old male patient (Schmidt, 2008).

A Brazilian qualitative study explored nurses' views on NPIs and reported that they used dialogue, a comfortable bed, a comfortable and quiet environment, recreation (such as blowing latex gloves into balloons), emotional support, and fluid intake to ease pain during SCC in children and adolescents (Campelo et al., 2018). Another qualitative study explored healthcare professionals' perspectives on the use of NPIs for SCD-related pain (Neri et al., 2016). Although the healthcare professionals had a positive attitude towards NPIs, they reported they did not use these interventions in SCD pediatric patients. The participants identified the following as barriers to the use of NPIs in practice: lack of process for integration of NPIs into practice, inadequate time and resources for NPIs being transitory due to short-term funding (Neri et al., 2016). In addition, no healthcare professionals were confident in their knowledge about NPIs, and they were interested in learning more about these interventions. Finally, in a US-based qualitative study, reported that hospitalized adolescents use music to manage their SCC pain at home but not in the hospital (Solodiuk et al., 2020). The participants reported that music was helpful for pain relief, distraction, and relaxation, and made them feel understood or connected with others.

Interventions at home

Six studies described the various NPIs used to manage SCC at home (Table 2). Only four were summatively analyzed, i.e., three cross-sectional studies and one qualitative study (Ali, 2014; Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006). These four studies included 156 participants in total. Only one study involved

adolescents with SCD (Ali, 2014); all other studies focused on parents/guardians of children and adolescents living with SCD. All studies allowed participants to select more than one intervention, and the total number of responses across the studies was 312 (Fig. 6). The most common interventions used were prayer, massage, and distraction (Fig. 6). A longitudinal study that included 18,377 diary days of 37 children and adolescents reported that sleeping/napping, massage, and heat application were the most frequently used interventions (Dampier et al., 2004). Higher pain intensity was associated with increased use of four NPIs: sleeping/napping, massage, heat, and relaxation/meditation/self-hypnosis (Dampier et al., 2004). Only Beyer and Simmons (2004) reported on the effectiveness of the interventions from the caregivers' perspective. They ranked massage, heat application, fluids, and prayer as the most effective interventions. Yoon and Black (2006) reported that the use of NPIs was significantly higher in caregivers whose children were taking two or more analgesics compared to children using one or none. In a qualitative study, Cotton et al. (2012) found that children used prayer to manage SCC, and they believed that prayer, sometimes, takes their pain away or God comforted them when they were in pain.

Discussion

This is the first scoping review on the various NPIs used in managing SCC pain in pediatric patients. No systematic review focusing on the effectiveness of any NPIs for SCC pain management were identified. Rather, those reviews that were found during the search focused on chronic pain or, general SCD pain, with no review targeting SCC pain. This scoping review shows that there has been an increase in number of studies on SCC acute pain over time. Before 2001, based on the included studies, there was only one study on the impact of NPIs on SCC pain (Cozzi et al., 1987). Between 2001 and 2011, there was an 800% increase compared to the previous decade, and, in the next decade, there was 900% increase compared to the previous decade. This indicates a significant increase in research focusing on NPIs to treat SCC pain in children over the past three decades. This surge may be due to an increased interest in the use of NPIs to provide optimal pain relief for SCC pain.

It was notable that most of the studies on NPIs use for SCC pain in pediatric patients with SCD were conducted in high-income countries, especially in the United States. Whilst unsurprising, it denotes the wide disparity existing across global regions in this field of research. This is a significant issue for research as the USA is economically and culturally very different from Africa, where most patients are affected. In this review, only one study was conducted in sub-Saharan Africa, specifically in Nigeria. With >75% of the global burden of SCD being in sub-Saharan Africa and the birth of 150,000 infants occurring annually in Nigeria, this is a concerning finding. This may be due to various reasons including lack of funding for research, a lack of prioritization of SCD management due to focus on infectious diseases such as malaria, or that the focus of SCC pain management is still mainly pharmacological in LMICs. Despite these challenges, there is a need for governments, researchers, and funding agencies in LMICs to prioritize resources for research on SCD. Considering that majority of pediatric patients with SCD live in LMICs, SCC pain with a focus on NPIs should be considered a priority to uphold the fundamental human right of pain relief of every SCD patient. This is crucial because NPIs are mostly inexpensive, are less reliant on specific resources unlike medications and are commonly used at home to manage SCC pain.

This review identified a major contrast between the NPIs used in hospitals versus those used at home. Out of the six studies focusing on the use of NPIs for SCC pain in hospitals, only two studies sought to identify the various NPIs used in hospitals, and they were both conducted in LMICs (Campelo et al., 2018; Oshikoya et al., 2015). The remaining four studies focused on specific interventions and healthcare professionals' attitudes towards NPIs, and they are all from high-income countries (Neri et al., 2016; Schmidt, 2008; Solodiuk et al., 2020; Tsai et al., 2020).

Table 2
Characteristics of the included studies.

#	First author (year)	Country	Study Design	Number of participants	Age (mean)	Intervention	Pain measure	Results
Experimental studies								
1	Bhushan et al., 2015	United States	Quasi-experimental study	2 patients with SCD hospitalized with SCC pain	13–17	Acupuncture	Questionnaire on the impact of acupuncture on pain management, need for medications, and perceived side-effects	Pain reduction was achieved but statistical significance could not be assessed. Patients were willing to use acupuncture in the future.
2	Cozzi et al., 1987	United States	Quasi-experimental study	8 patients with SCD	10–20	Biofeedback-Assisted Relaxation	5-point scale	*Significant reductions in headaches ($p < 0.05$), frequency of self-treated crises, pain associated with self-treated crises ($p < 0.001$), and the number of days participants used analgesia ($p < 0.01$). Authors indicated no significant reductions in inpatient hospitalizations and emergency room visits; the intervention may only be useful for milder crises (headaches, limb pain).
3	Diaz-Hennessey et al., 2019	United States	Quasi-experimental study	15 patients with SCD hospitalized with SCC pain	8–17 (13)	Virtual reality	FLACC Behavioral Pain Assessment Scale Self-report Numerical Rating Scale	No significant reduction in pain intensity and pain medication consumption in intervention group vs control group. Intervention group reported higher mean pain scores. Reduction in FLACC scores and the average length of hospitalization (not significant).
4	Dobson, 2006	United States	Quasi-experimental study	20 patients with SCD	6–11 (mean: 8.4)	Guided Imagery	Investigator-designed pain profile FACES pain scale	*Significant reduction in pain intensity ($p = 0.00$) and frequency of pain episodes ($p = 0.003$). Decreased analgesics use, and ibuprofen was often used instead of opioids.
5	Reece-Stremtan et al., 2021	United States	Quasi-experimental study	29 patients with SCD and their parents hospitalized for SCC pain	Mean: Intervention group: 16.4 Control group: 16.3	Acupuncture	Numerical rating scale	*Significant reduction in pain intensity ($p < 0.001$). Deemed acceptable by 66% of the participants. Reduction in length of hospitalization and readmission rates, but not statistically significant. No side-effects.
6	Agrawal et al., 2019	United States	Quasi-experimental study	30 patients with SCD hospitalized for SCC pain	13.3–20 Median: 16.0	Virtual reality	Adolescent pediatric pain tool (APPT)	*Significant reduction in pain intensity ($p < 0.001$) and number of body parts affected by SCC ($p < 0.001$). Deemed acceptable by the participants. No side effects.
7	Sil et al., 2021	United States	Quasi-experimental study	57 patients with SCD hospitalized for SCC pain	8–18 (13.3)	Cognitive-behavioral therapy	The Knowledge of Psychological Interventions for Pain	*Significant improvements in knowledge of pain management techniques ($p < 0.001$). Accepted by the participants.
8	Wihak et al., 2020	United States	Quasi-experimental study	8 patients with SCD hospitalized for SCC pain	10–17	Video-based cognitive behavioral therapy intervention	Not assessed	Intervention was highly acceptable to adolescents and parents and can be administered during an inpatient hospitalization or a routine outpatient appointment.
9	Schatz et al., 2015	United States	Randomised controlled trial	46 patients with SCD	8–21 (13.04)	Smartphone-based cognitive behavioral therapy	Pain History, Interview Electronic Daily Pain and Activity Diary (DPAD)	Increased beliefs in pain controllability, but negative thinking in response to pain was unchanged. Reduction in next-day pain intensity when the participants used the intervention for higher pain, compared to days they did not use the intervention.
10	Chiami, 2015	United States	Randomised controlled trial	30 patients with SCD hospitalized for SCC pain	4–14 Intervention: 8.2 Control: 7.9	Music	Wong-Baker Faces Scale	Reductions in pain, but not statistically significant.
11	Hood et al., 2021	United States	Randomised controlled trial	26 patients with SCD	13–21 (16.7)	Cognitive-behavioral therapy (a mobile app called iManage for SCD)	Pain diary on the iManage mobile app	The participants used these interventions: rest, fluids, distraction techniques, and a warm heating pad. The participants who engaged with the mobile app had statistically significant reduction in

(continued on next page)

Table 2 (continued)

#	First author (year)	Country	Study Design	Number of participants	Age (mean)	Intervention	Pain measure	Results
12	Barakat et al., 2010	United States	Randomised controlled trial	27 patients with SCD hospitalized for SCC pain and their parents	12–18 (14.24)	PAIN consisted of training in deep breathing/relaxation, positive coping statements, and guided imagery.	a daily paper-and-pencil pain diary	pain and better mood symptoms. No significant reductions in pain between the intervention and control groups.
13	Schwartz et al., 2007	United States	Randomised controlled trial	49 patients with SCD	12–18 (14.32)	Cognitive-behavioral therapy (home-based pain management intervention)	Not measured	Feasible for pain management and endorsed by all except one participant.
14	Moody et al., 2017	United States	Randomised controlled trial	73 patients with SCD hospitalized for SCC pain and their parents.	6–21 (15)	Yoga	Wong-Baker FACES® Pain Rating Scale for children	*Significant reduction in pain after the first session ($p = 0.02$) but subsequently, there was some reduction, but it was not statistically significant. Yoga is an acceptable and feasible intervention for hospitalized children with SCC.
15	Braniecki, 2003	United States	Randomised controlled trials	16 patients with SCD and their caregivers.	10–17 (13.88)	Guided imagery	Pain diary; Vami/Thompson Pediatric Pain Questionnaire	No significant changes in pain intensity and decrease in the number of pain reports in the intervention group compared to the control group.
Non-experimental studies								
16	Schmidt, 2008	Chile	Case report	1 patient with SCD experiencing SCC pain	10	Guided imagery	N/A	Reduction in pain intensity and deemed acceptable by the participant.
17	Beyer & Simmons, 2004	United States	Cohort study	21 Caregivers of children and adolescents aged 5 to 19 years hospitalized with SCC pain	25–45	N/A	N/A	Participants mostly used heat application, massage, and prayer. Rank based on effectiveness: Rubbing, Heat, Fluids, Prayer, Rest, Relaxation tapes, Relaxation tapes, Distraction (Rocking, Diversion, Drawing, Games, TV, video games, movies, and car ride)
18	Dampier et al., 2004	United States	Longitudinal study	39 patients with SCD	5.8–19.1 (mean: 10.9)	N/A	N/A	The NPIs the participants used were: watch TV/read, sleep/nap, hot bath/heating pad, massage, talk with people, pray and relaxation/meditation/self-hypnosis.
19	Oshikoya et al., 2015	Nigeria	Longitudinal study	120 patients with SCD hospitalized for SCC pain	3–9 (4 years)	N/A	N/A	The NPIs used by participants during emergency admission were fluid intake and prayers.
20	Smith et al., 2018	United States	Cross-sectional study	42 Caregivers of children aged 2–6 living with SCD	19–50	N/A	N/A	Participants used these NPIs: warm baths, massage, distraction, and using a hot or cold compress, progressive muscle relaxation. Though infrequently used, deep breathing and progressive muscle relaxation were often used together.
21	Ali, 2014	United States	Cross-sectional study	30 SCD adolescents hospitalized with SCC pain	12–21	N/A	N/A	Participants used these NPIs: rest/sleep, heat application, watching television, videogames, computer, yoga, reading, talking to people, playing with a dog, and "icy hot".
22	Yoon & Black, 2006	United States	Cross-sectional study	63 Caregivers of children living with SCD	Mean for parent: 33 years, and children: 9	N/A	N/A	Majority of the participants used at least one non-pharmacological intervention for their children in the past 6 months. The most used: prayer, spiritual healing by others, massage therapy, relaxation, megavitamins and herbal products, heat application, and warm baths.
23	Tsai et al., 2020	United States	Retrospective chart review	24 patients with SCD hospitalized with SCC pain	8–21 (17.5)	Acupuncture	4-point and 10-point Verbal Pain Scales	Reduction in pain intensity and deemed acceptable by the participants. Feasible in both the outpatient and inpatient settings.
24	Solodiuk et al., 2020	United States	Qualitative study	9 patients with SCD	12–21	Music therapy	N/A	Participants reported that music was helpful for pain relief, distraction, relaxation, and feeling understood or connected with others. However, they did not use music for pain

Table 2 (continued)

#	First author (year)	Country	Study Design	Number of participants	Age (mean)	Intervention	Pain measure	Results
25	Neri et al., 2016	Australia	Qualitative study	10 healthcare workers working with the Division of Haematology	Not stated	N/A	N/A	when hospitalized. Participants used music to create a preferred comforting environment which may be quiet, dark, loud, or bright when in pain. Other NPI identified include a physically warm environment, being in the company of friends or family members or positive hospital staff workers, and being alone. Participants generally had a positive attitude towards NPI. They do not optimally use them due to these barriers: the lack of process for integration of these interventions into conventional practice, lack of time, lack of provider comfort and training, and resources for NPI are often temporary due to short term funding. No participant was totally comfortable with their knowledge of NPI, and they desired to acquire knowledge on these interventions. The healthcare professionals used interventions such as recreation, dialogue and providing emotional support, a comfortable and quiet environment, hydration, and a comfortable bed.
26	Campelo et al., 2018	Brazil	Qualitative study	13 Nurses caring for pediatric patients with SCD	23–44 years	N/A	N/A	More than half of the children used prayer or religion to manage SCD. Most children believed prayer sometimes takes the pain away, and others believed it did. Few said it did not take the pain away. The children believed that, when they were in pain, God provided comfort for them.
27	Cotton et al., 2012	United States	Qualitative study	20 patients with SCD	5–10 (8.05)	Prayer	N/A	

N/A = not applicable/stated.
 * = Statistically significant results.

Therefore, these results may not accurately reflect the actual NPIs used in those various hospitals. In the Nigerian study, the authors specifically stated that only two NPIs were identified, that is, prayer and fluid intake (Oshikoya et al., 2015). Considering that clinical guidelines and

literature reviews have recommended numerous NPIs, the use of only two interventions among 120 patients is a relatively low number (Amid & Odame, 2014; Brandow et al., 2020; Lakkakula et al., 2018; National Heart Lung and Blood Institute, 2014; Telfer & Kaya, 2017;

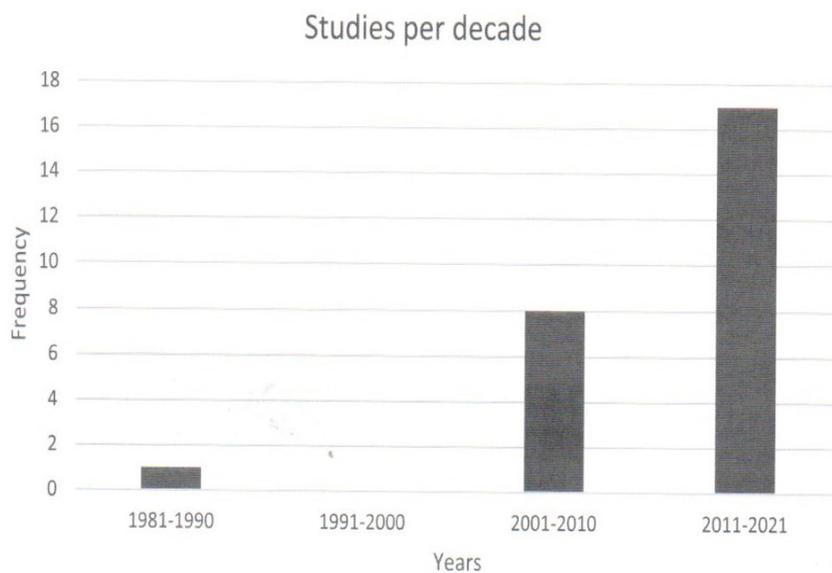


Fig. 3. Number of published studies per decade (1981–2021). This figure shows the number of included studies published per decade between 1981 and 2021.

Table 3
List of Non-pharmacological interventions (NPIs) identified in this review.

Category	Sub-category	Interventions	Studies	
Biomedical	Physical exercise Physical manipulative interventions	Deep breathing	Barakat et al., 2010; Smith et al., 2018	
		Massage	Yoon & Black, 2006; Beyer & Simmons, 2004; Dampier et al., 2004; Smith et al., 2018; Yoon & Black, 2006	
		Heat application	Beyer & Simmons, 2004; Dampier et al., 2004; Ali, 2014; Yoon & Black, 2006; Hood et al., 2021	
	Distraction	Hot/cold compress	Dampier et al., 2004; Smith et al., 2018	
		Reading	Ali, 2014	
		Playing with dog	Ali, 2014	
		Dialogue	Campelo et al., 2018; Dampier et al., 2004	
		Virtual reality	Diaz-Hennessey et al., 2019; Agrawal et al., 2019	
	Other biomedical NPIs	Music	Chiami, 2015; Solodiuk et al., 2020	
		Fluid intake	Beyer & Simmons, 2004; Oshikoya et al., 2015; Hood et al., 2021; Campelo et al., 2018	
		Sleep/rest	Dampier et al., 2004; Ali, 2014; Hood et al., 2021; Beyer & Simmons, 2004	
		Icy-hot	Ali, 2014	
		Comfortable bed	Campelo et al., 2018	
Comfortable and quiet environment		Campelo et al., 2018		
Recreation		Campelo et al., 2018		
Alternative Health	Alternative health belief systems	Emotional support	Campelo et al., 2018	
		Relaxation	Barakat et al., 2010; Beyer & Simmons, 2004; Dampier et al., 2004; Smith et al., 2018; Yoon & Black, 2006	
	Herbal and nutritional interventions,	Warm bath	Hood et al., 2021; Smith et al., 2018; Yoon & Black, 2006	
		Prayer	Beyer & Simmons, 2004; Oshikoya et al., 2015; Yoon & Black, 2006; Cotton et al., 2012; Dampier et al., 2004	
	Mind-body interventions	Acupuncture	Bhushan et al., 2015; Reece-Stremtan et al., 2021; Tsai et al., 2020	
		Herbal supplements/products	Yoon & Black, 2006	
	Combined	Mind-body interventions	Megavitamins	Yoon & Black, 2006
			Biofeedback	Smith et al., 2018
		Other biomedical NPIs	Guided imagery	Dobson, 2006, Schmidt, 2008; Barakat et al., 2010
			Biofeedback-assisted relaxation	Cozzi et al., 1987; Wihak et al., 2020; Schatz et al., 2015; Sil et al., 2021; Schwartz et al., 2007
Other biomedical NPIs	Cognitive-behavioral therapy with multiple components	Wihak et al., 2020; Schatz et al., 2015; Sil et al., 2021; Schwartz et al., 2007		
	Yoga	Moody et al., 2017; Ali, 2014		

Zempsky, 2010). While this may not represent the situation in the whole country of Nigeria, it is still worth exploring if pediatric patients, their families, and healthcare professionals are aware of other NPIs. This situation is not limited to LMICs. In a US-based study, Solodiuk et al. (2020) reported that adolescents used music for the management of SCC pain at home but did not use it in the hospital. Therefore, are

there barriers preventing the use of certain NPIs while in the hospital? Though, as a whole, the studies reported 17 different interventions were being used at home in the United States, we wonder if patients use these interventions when they are hospitalized. No study from the United States identified the various interventions used at home. Future studies should explore these questions because their findings can help

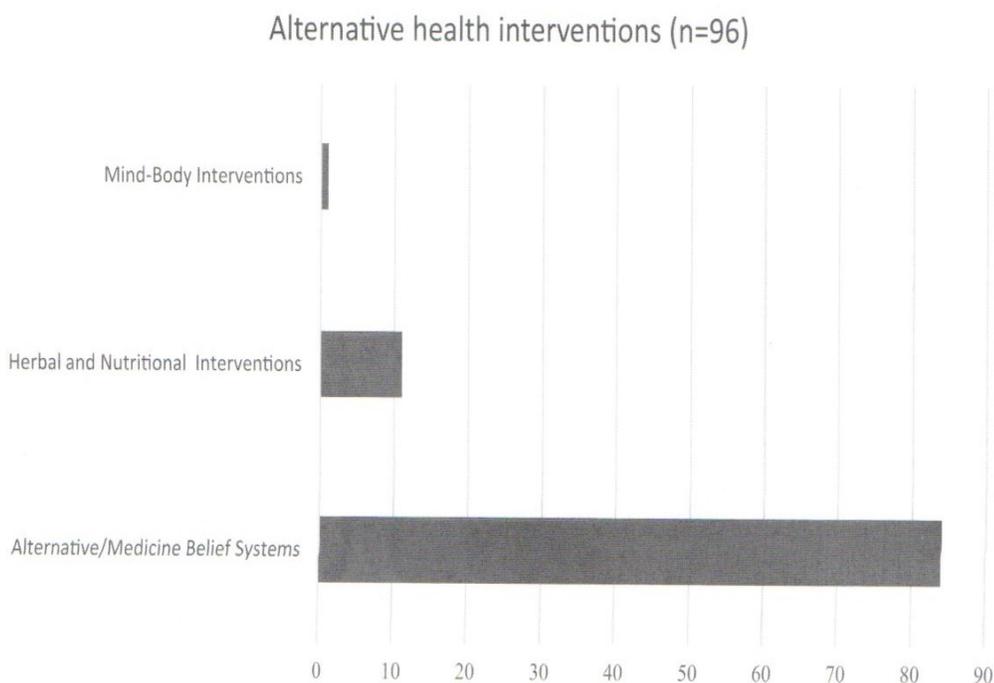


Fig. 4. Alternative health interventions used by patients. This figure depicts the number of participants using various alternative health interventions. These results are based on the findings of four studies. (Ali, 2014; Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006). All studies were conducted in the United States. In these studies, participants were allowed to choose more than one intervention.

Biomedical non-pharmacological interventions (n=215)

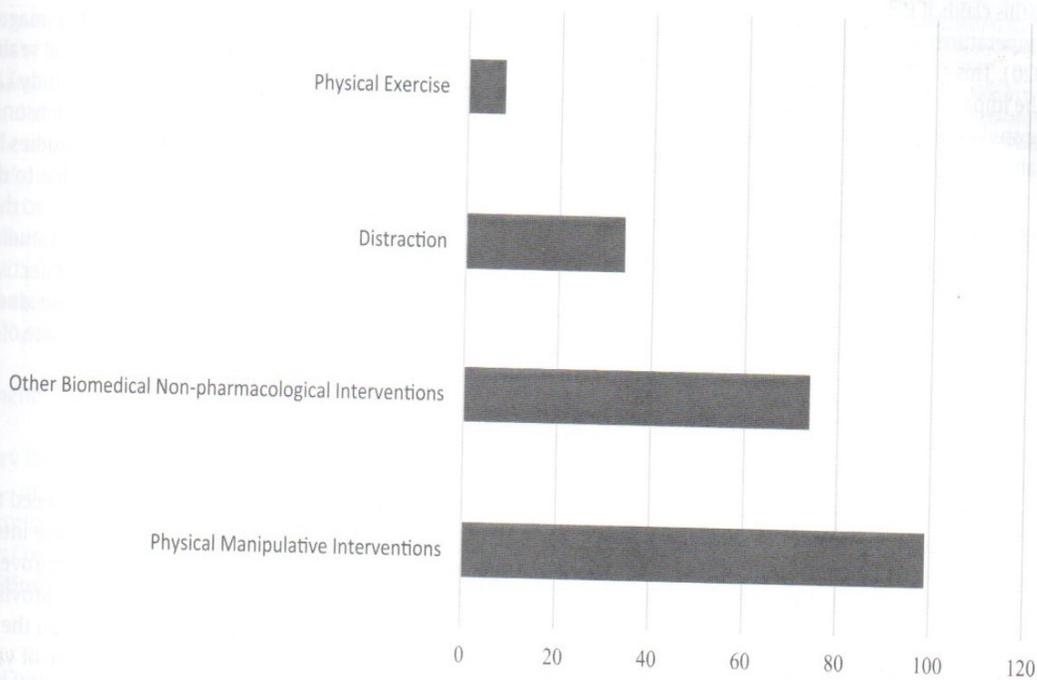


Fig. 5. Biomedical non-pharmacological interventions used by patients. The figure depicts the number of participants using various biomedical NPIs. These results are based on the findings of four studies. (Ali, 2014; Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006). All studies were conducted in the United States. In these studies, participants were allowed to choose more than one intervention.

identify barriers and improve SCC pain management within the hospital setting.

Furthermore, this scoping review identified a wide range of NPIs used at home to manage SCC pain. All the studies in this category were conducted in the United States (Ali, 2014; Beyer & Simmons, 2004; Cotton et al., 2012; Dampier et al., 2004; Smith et al., 2018; Yoon & Black, 2006); hence these findings are more reflective of the practice in the United States than in other countries. It is imperative for researchers in LMICs, particularly in countries with high prevalence

and mortality rates of SCD, to investigate what interventions are used at home to manage interventions. This is important because some interventions may be contributing to negative patient outcomes unbeknownst to the patients and their families. A typical example is cold compression, the application of cold packs to painful areas. In this review, cold application was the seventh most common intervention used at home for SCC pain management, and it has also been recommended in a literature review (Ballas, 2011). However, DeBaun (2021) cautioned that cold compressions might precipitate sickling of

Non-pharmacological interventions used at home (n=312)

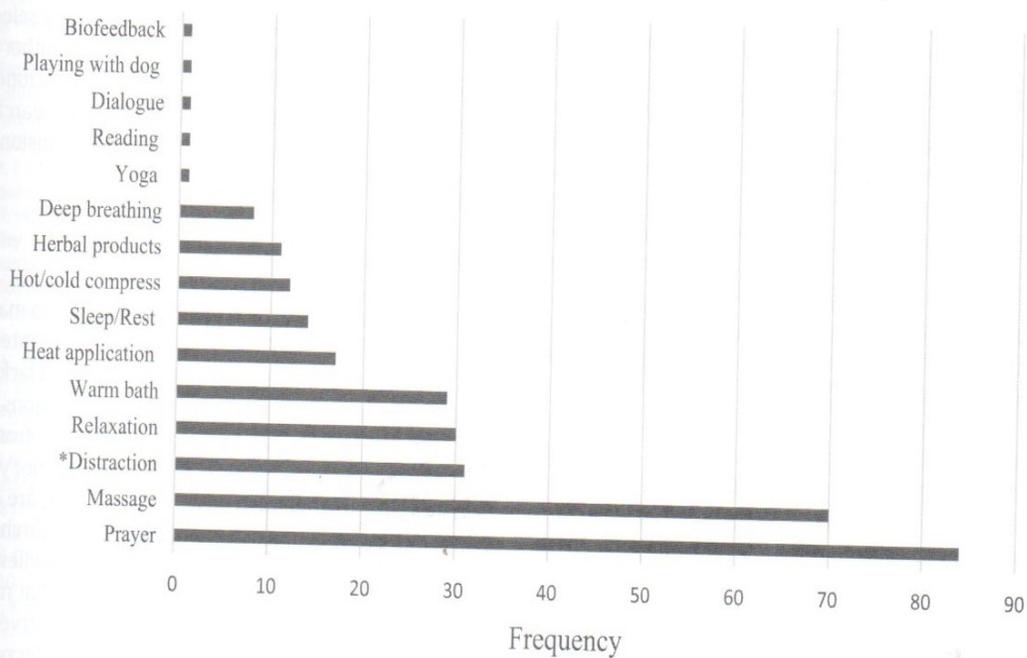


Fig. 6. Non-pharmacological interventions used at home. The figure depicts the number of participants using various NPIs based on the results of 4 studies (Ali, 2014; Beyer & Simmons, 2004; Smith et al., 2018; Yoon & Black, 2006). All studies were conducted in the United States. In these studies, participants were allowed to choose more than one intervention. *Distraction include: watching TV and Videogames.

erythrocytes; hence, it should be avoided. Whilst no evidence was stated to support this claim, it is theoretically understandable considering that cold temperatures are triggers of SCC (Ballas et al., 2012; Darbari et al., 2020). This finding further corroborates the importance of ascertaining the impact of these home interventions on SCC and its pain. Conducting studies on home pain management can help determine if appropriate interventions are being used and determine the effects of the interventions on SCC pain, frequency of SCC, and the incidence of complications, as well as identify possible educational needs.

The effectiveness of most interventions used at home has not been explored through research. Additionally, only one study reported on the effectiveness of these interventions from the patients' perspectives (Beyer & Simmons, 2004). According to this study, the most effective interventions are massage, heat application, fluid intake, and prayer. However, no study was found that ascertained their effectiveness through robust scientific methods. These interventions, except prayer, are also widely recommended by expert panels and authors of literature reviews (Amid & Odame, 2014; Brandow et al., 2020; Lakkakula et al., 2018; National Heart Lung and Blood Institute, 2014; Telfer & Kaya, 2017; Zempsky, 2010). Massage and heat application are the first and second most recommended interventions by expert panels and authors of literature reviews (Amid & Odame, 2014; Brandow et al., 2020; Lakkakula et al., 2018; National Heart Lung and Blood Institute, 2014; Telfer & Kaya, 2017; Zempsky, 2010). Brandow et al. (2020) opined that these interventions could be used since they have a low risk of harm, but the interventions should be tailored to the patients' needs and preferences. Nonetheless, it remains essential to determine whether these interventions are effective or provide a placebo effect. It is worth noting that some interventions may be more difficult to investigate in a robust experimental study, such as is the case for prayer, for example. Prayer is the most commonly used NPI at home, and in one study, it was the most commonly used in hospitals (Oshikoya et al., 2015). This finding may be due to the overwhelming nature of SCC pain, so much so that patients with SCD seek alternative ways, such as a higher power, to heal them from a pain that is not fully responsive to current pharmacological interventions. It is also worthy of note that no clinical guidelines and literature reviews recommended prayer as an NPI. It is unclear why it was not recommended. Some may argue that it has not been shown to be an effective strategy but so are many other interventions recommended by these clinical guidelines. Regardless, it is vital for healthcare professionals to recognize that pediatric patients with SCD rely on prayer as an intervention to manage their pain.

The most common category of interventions used by patients was biomedical NPIs. While it is unclear why pediatric SCD patients tend to use these interventions more often, it may be borne out of curiosity to explore a wide range of interventions to identify an effective pain reliever. Additionally, massage (a simple physical intervention to improve circulation and relax muscles) seems to be used very frequently. It was unclear how the massage was provided and what substances (such as ointment) were used in the reported work. However, it may be helpful for massage therapists to educate patients and their families on various massage techniques targeted for SCC pain, and for researchers to evaluate the most effective massage techniques for SCC pain.

Furthermore, the use of Garrett et al.'s categorization for alternative therapies (Garrett et al., 2021) was helpful in summarizing the findings. However, as with any system, there was some overlap. Some interventions could be classified in more than one category and hence a combined classification was also used. A typical example was yoga, which was classified as an alternate health spiritual intervention but also involves gentle exercise, which falls under biomedical interventions. It can be challenging to classify these interventions, but it is useful to separate the nature of the interventions in terms of their basis in biomedical science or otherwise. Hence, this review classified these interventions as indicated in Table 3 (Garrett et al., 2021).

It was notable that there were relatively few experimental studies exploring the effectiveness of specific interventions on SCC pain management in children and adolescents. Only guided imagery, cognitive-behavioral interventions, acupuncture, and virtual reality have been tested on their effectiveness in more than one study (Barakat et al., 2010; Bhushan et al., 2015; Braniecki, 2003; Dobson, 2006; Hood et al., 2021; Reece-Stremtan et al., 2021). These studies have inconsistent results, and a meta-analysis was not possible to determine the pooled effect of these interventions on SCC pain due to their low prevalence. There is a critical need for more experimental studies on these interventions, and other NPIs, to determine their effectiveness on SCC pain in this patient population. Furthermore, future studies should investigate appropriate NPIs for children below the age of 4, as no study within this age group was identified.

Practice implications

The results of this scoping review present the need to improve the use of NPIs for SCC pain in clinical settings as these interventions can aid in achieving optimal pain relief. These improvements can be achieved through education, advocacy, and the provision of various NPIs in hospitals. Clinicians should be educated on the importance of NPIs in SCC pain management and the existence of various types of safe and recommended NPIs. During hospital admissions, clinicians can encourage patients experiencing SCC to use safe and effective NPIs that they usually use at home. Clinicians can introduce patients and their families to various NPIs that can be beneficial for alleviating pain during SCC. Nurses play a vital role in clinical pain management hence advocating for the use of NPIs might improve patient access to these interventions in hospitals. Also, it is important for hospital management to prioritize training on NPIs for clinicians, patients, and their families and provide the resources necessary to implement these interventions in practice.

Limitations

This scoping review has its limitations. Despite the extended efforts to include every eligible study, relevant studies may have been missed. Also, research articles written in other languages were excluded; hence vital articles may have been missed due to this exclusion. Also, 11 studies that may have been relevant to the review were excluded because full texts were unavailable. Additionally, the study selection, data extraction, and analysis were conducted by only one author (BMI). Despite these limitations, this study has strengths which include: an extensive search across nine databases using a rigorous search strategy co-developed with a university librarian and the inclusion of a relatively high number of studies.

Conclusion

Pediatric patients with SCD use numerous NPIs to manage their pain during a sickle cell crisis; however, many of these interventions have not been empirically investigated. Hence, there is a lack of reliable evidence to justify the effectiveness of these interventions. SCC pain has a unique pathophysiology and generalizing research from other patient populations experiencing acute pain episodes may not yield the desired pain outcomes. High burden areas, such as LMICs, are especially challenged by the lack of research prioritization by researchers and funding agencies on the use of NPIs for SCC pain. Future studies should explore the use of NPIs in hospitals and identify barriers that may hinder their use. There is a need to develop educational interventions on NPIs targeted at healthcare professionals providing care for pediatric patients with SCD. Hospital stakeholders and decision-makers should have conversations with healthcare professionals to understand and mitigate

barriers to the use of NPIs and optimal pain management for this patient population.

Overall, there is currently inadequate evidence to support the clinical effectiveness of any NPI for pain management during sickle cell crisis in pediatric patients. This deficiency is more profound in LMICs, where no experimental study was identified. Given the low cost and ease of use, NPIs can be useful in low-resource settings challenged with poor access to opioids, weak health infrastructure, and poverty. Healthcare professionals and researchers must be aware that SCD pain is a lifelong pain condition with detrimental effects on the individual's social, emotional, physical, and mental well-being. Hence, every effort should be made to make their pain experience as less painful as possible, and NPIs can be useful in achieving this optimal pain relief.

CREDIT Statement

Bukola Mary Ibitoye: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Bernie Garrett:** Conceptualization, Writing – review & editing, Supervision. **Manon Ranger:** Conceptualization, Writing – review & editing, Supervision. **Jennifer Stinson:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pedn.2023.03.002>.

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