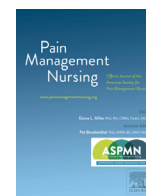




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Multimodal pain management of children with OI

Multimodal Pain Management of Children Diagnosed with Osteogenesis Imperfecta: An Integrative Literature Review

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ABSTRACT

Objectives: The objective of this literature review was to evaluate multimodal therapies and interventions that help prevent progression and manage pain in children with OI.

Design: A systematic review of literature utilizing PRISMA guidelines.

Data sources: The Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete, PubMed, PsycINFO, UpToDate, and ProQuest Nursing & Allied Health Source.

Review/Analysis methods: Existing literature on pain management in pediatric patients diagnosed with OI was reviewed and appraised. Fifteen studies met the criteria for review.

Results: Results indicated that therapies addressing pain management are most effective when they use a multimodal approach that promotes bone strength, psychological support, reduces the risk of fractures, increases bone stability, and maintains physiological function. Four multimodal treatments for pain management in children with OI were identified including bisphosphonate therapy, surgical intervention, physical therapy, and psychosocial support.

Conclusions: Developing a finite understanding of the utilization of multimodal therapies to manage and treat pain can assist in engineering treatments that improve the quality of life for children diagnosed with OI.

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Osteogenesis imperfecta (OI) is the most common heritable bone disorder in children, affecting about 50,000 individuals in the United States (Trejo & Rauch, 2016). Characterized by bone fragility caused by a lack of collagen that forms the bone matrix, OI leads to fractures, spinal deformity, and affects other organs (Trejo & Rauch, 2016). There are various types of OI that range in severity; nonetheless, any type of OI can diminish a child's quality of life by causing skeletal deformity, fractures, and long-term disability (Tsimicalis et al., 2018).

A hallmark symptom of OI is pain. Factors such as recurrent fracture, bone deformity, muscle atrophy, mobility limitations, and psychological factors, can all impact a child's pain experience. Pain is defined as a "multidimensional sensation containing physiological, cognitive, behavioral, environmental, and spiritual components" (World Health Organization, 2012). Pain is further divided into two contexts: acute or chronic. Acute pain refers to an unpleasant sensation with quick onset and a limited duration, which often occurs in conjunction with impending tissue damage. Acute

pain can further develop into chronic pain as recurrent fractures may result in skeletal malformations (Nghiem et al., 2017). Chronic pain may occur without immediate tissue damage, persists for more than three months, and has a continuous ongoing duration that requires specialized care (Treede et al., 2019).

Subtypes of OI are classified based on clinical features and disease progression; types I, III, and IV are discussed in this review. Type II OI is not included in this review as it results in death during the perinatal period due to the severity of the disease. Type I OI is the mildest form of the disease with normal growth patterns and a low incidence of fracture in the prenatal period. Type III is a more severe form of OI. Individuals with type III OI may sustain fractures during birth, demonstrate severe bone deformity, and have a high incidence of fractures throughout adulthood. Type IV OI is the most clinically diverse group, with individuals exhibiting mild to severe symptoms (Roughley, Rauch & Glorieux, 2003).

Acute and chronic pain are persistent features in OI manifesting in the initial phases of tissue damage and lasting through long-term fracture healing. Opioid-based therapy is utilized for pain management traditionally, although studies suggest there are benefits to utilizing multimodal therapy in conjunction with pharmacologic pain management (Vanz & Lee, 2018). Reducing bone fragility

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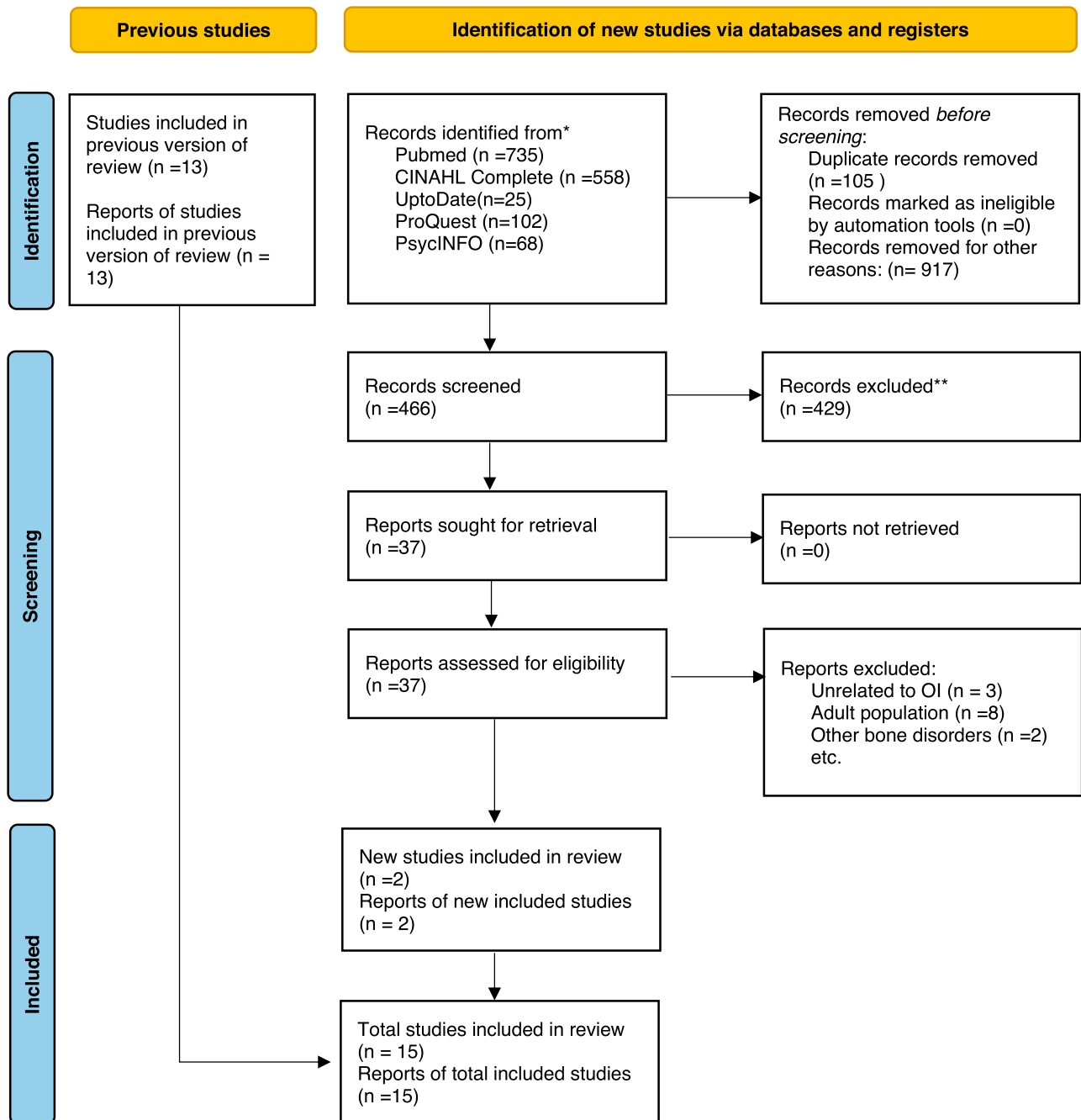


Fig 1. Literature Search Process and Results utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.

and preventing bone fractures, while maximizing mobility supports good quality of life in those diagnosed with OI (Tsimicalis et al., 2018). Employing multimodal therapy (anti-resorptive drugs like bisphosphonate, surgical treatments, and physical therapy) as well as opioid-based pain management are believed to contribute to reducing the overall pain experience (Mueller et al., 2018).

Objective

The objective of this literature review was to evaluate multimodal therapies and interventions that help prevent and manage pain in children with OI. Findings of this review could promote insight into developing multimodal therapies that help manage complex pain experiences in children with OI.

Design And Data Sources

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to structure this integrative literature review (Page et al., 2021). In January 2019, a comprehensive literature search was conducted. The literature was systematically searched and analyzed to help determine significant findings regarding multimodal pain management strategies for this disorder (see Fig. 1). The comprehensive literature search was conducted using the following databases: The Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete, PubMed, PsycINFO, UpToDate, and ProQuest Nursing & Allied Health Source. Subject terms were utilized to yield studies for review. Reference lists from

included research studies were also examined for additional papers not found in the initial databases search. We searched each database for the following terms: osteogenesis imperfecta in pediatric populations, brittle bone disorder, treatment for osteogenesis imperfecta, pain management, pain quality, alternative therapies, long-term pain management, nursing intervention, bisphosphonate therapy, and fractures. Terms excluded by the reviewers included osteoporosis, adult populations, and coexisting conditions with OI.

The study inclusion criteria included papers: (1) published in a peer reviewed journal; (2) written in the English language; and (3) including a study population with ages 2 to 21 years. Exclusion criteria were studies: (1) conducted on adults; (2) examining other bone disorders not including OI; (3) studies not relating to pain response. Duplicate articles were removed, and remaining articles were reviewed excluding articles that did not pertain to the topic. Articles were screened independently by two reviewers experienced in critical analysis of literature, to determine eligibility for inclusion based on previously determined criteria. After the screening process, the articles not meeting inclusion criteria (not directly related to pain, included adult populations, or did not directly address the research question) were excluded. The remaining full text articles were assessed for eligibility, yielding the final reviewed studies. Additional studies were reviewed and included after the initial review period during a secondary referencing of relevant studies.

Data Presentation

The resulting data were categorized and presented in [Table 1](#) listed by author, research question, sample population, methods, design, findings, and relevance.

Results

A total of 1,488 articles were found through the initial search process. A total of 15 full text articles were selected for inclusion in the literature review. The findings highlighted in this review identified various therapies that can be utilized for pain management or fracture prevention, in children with OI. These included bisphosphonate therapy, surgical intervention, occupational and physical therapy, and psychosocial support. The results from this search are presented in [Table 2](#).

Bisphosphonate Therapy

Bisphosphonate therapy is a pharmacologic intervention utilized in pediatric patients that is often indicated in patients sustaining two or more fragility fractures per year. Common forms of bisphosphonates include pamidronate or zoledronic acid, which work by decreasing bone turnover, improving bone mineral density, and reducing fracture rate ([Garganta et al., 2018](#)). Pain in children receiving bisphosphonate therapy was studied in a retrospective longitudinal cohort study consisting of 22 children with OI. Participants received either pamidronate infusions every 3 to 4 months, or zoledronic acid infusions every 6 months. Physical function and pain scores were recorded before infusion, and 4 weeks after infusion. Results indicated a reduction in pain postinfusion, in addition to a decrease in pain reported weeks following the initial infusion ([Garganta et al., 2018](#)). Bisphosphonate treatment was also shown to improve physical functioning, and self-care behavior, and promote more physical independence. Unfortunately, the pain relief seemed to have a short-term effect, with the initial pain returning after 4 weeks following each infusion ([Garganta et al., 2018](#)).

Bisphosphonate therapy demonstrates a positive effect on the prevention of scoliosis as children age. Prevention of scoliosis can aid in decreasing chronic pain and deformity in children. Data were collected over 15 years in a retrospective study consisting of 37 children, it was found that treatment with intravenous bisphosphonate aided in reshaping compressed vertebral bodies ([Palomo et al., 2015](#)). This suggested that the utilization of bisphosphonate therapy may slow progression of scoliosis, however, it may be ineffective in the prevention of scoliosis in children with more severe forms of OI ([Palomo et al., 2015](#)). A retrospective, longitudinal study of 52 children with various forms of OI was conducted to examine the relationship between scoliosis development in children when undergoing treatment with oral bisphosphonates or intravenous pamidronate. Results suggested development of scoliosis was widely dependent of severity of OI. Early intervention with intravenous pamidronate improved vertebral fragility and could potentially decrease progression or incidence of scoliosis if initiated during infancy or early in childhood ([Kashii et al., 2019](#)). In a controlled clinical trial of 18 children with OI types III and IV treated with intravenous pamidronate, patients demonstrated an increased lumbar spine bone mineral density, midvertebral height, and total vertebral area, when compared with the control group treated with the placebo ([Letocha et al., 2005](#)). There was a significant reduction in upper extremity fractures, but no reduction in lower extremity fracture rate. Results were variable throughout participants with no significant improvement of pain, ambulatory status, or growth rate ([Letocha et al., 2005](#)).

Results on the effects of the use of pamidronate in children with OI demonstrated improved bone density, mobility, reduced fracture frequency, and increased walking ability. Biomarkers of osteoclast activity released from bone matrix remodeling were reduced by 25%. This indicated the effectiveness of the bisphosphonate therapy with preservation of the bone matrix and improvements in bone metabolism ([Marginean, Tamasanu, Mang, Mozos, & Brad, 2017](#)). In a qualitative study involving 12 children with OI, some negative physical symptoms were often reported prior to cyclic infusions such as fatigue, bone pain, and sleep interruptions. Many participants described a “renewal” experience or enhanced wellbeing post infusion. ([Wiggins & Kreikemeier, 2017](#)).

Surgical Intervention

Surgical rodding is a procedure that is primarily utilized for the fixation of long bones. This prevents fractures and deformity within the bone, while maximizing motor function and development ([Bhaskar and Khurana, 2019](#)). Characteristic deformities of OI, such as bowing of the tibia, can arise from muscle forces acting on weak or fractured bone, leading to a cycle of fracture and re-fracture. Excess loading forces on fractured bone can increase the rate of bone remodeling leading to cortical thickening of bone and stress shielding. This in turn can lead to bone deformity, pain from fracture, and decreased ambulatory potential ([Bhaskar and Khurana, 2019](#)). In a retrospective study of individuals with OI, aged 3 to 21, who had received rodding procedures, there was a significant reduction in fracture rate. Prior to stabilization by rodding procedures, the refracture rate was 2.3 fractures per child each year. Following surgery, there was no recurrence of fractures in any of the participants within the study, in addition to an increase in muscle strength and independent ambulation ([Bhaskar and Khurana, 2019](#)).

In a retrospective chart review of children with OI types I and III results of upper extremity rodding procedures were observed involving fixation of intramedullary rods within the humerus and forearm. Orthopedic procedures performed on the upper extremities promoted realignment and reduced fracture

Table 1
Summery Table of Published Studies Included in Literature Review

Author (y)	Purpose/ Research question	Sample population	Methods	Research design	Findings/Outcomes	Relevance
Garganta et al. (2018)	Examining the effect of cyclic intravenous bisphosphonate treatment on children with OI using patient-reported pain levels and parent-assessed physical functioning over time	Children with OI types I, III, and IV (n = 22)	Pain response and physical functioning were assessed at multiple intervals over two bisphosphonate infusion cycles	Prospective longitudinal cohort study	Cyclic intravenous bisphosphonate therapy reduces pain and improves functional abilities Pain relief occurs immediately following infusion with improvements in functional status Long-term pain relief and effects not observed within the study	The direct effect of utilizing cyclic bisphosphonate therapy for acute and chronic pain management of OI in pediatric patients
Hoyer-Kuhn et al. (2014)	The goal was to evaluate the effectiveness of new physiotherapy approaches and whole-body vibration on motor function in children with OI	53 Children with OI (n = 53)	Children participated in a 12-month program The first 6 months consisted of alternating whole-body vibration, treadmill training, as well as exercise training Follow up results were analyzed 6 months after completion of the program	Retrospective study	Increase in motor function, walking ability, and bone mineral density (not including the head and neck)	The role of exercise programs in pain management and motor function in children with OI
Bhaskar & Khurana. (2019)	Review the direct effect of ambulation and rate of fracture in children with OI that underwent intramedullary rodding procedures	21 Children with OI (n = 21)	Ambulatory status was assessed by the Hoffers and Bullock's grading Ambulatory status, pain, and ability for independent self-care were assed postoperatively in a period of 24-48 months	Retrospective review	Intramedullary rodding improves mobility potential, prevents repeated cast application, disuse wasting, and osteopenia in children with OI	Direct effect of orthopedic surgical intervention on ambulation and pain quality in children with OI
Marginean, Tamasanu, Mang, Mozos, & Brad. (2017)	Present findings and investigate the evolution of treatment in patients diagnosed with OI	9 Children with OI (n = 9)	Assessing impact of OI in children by clinical evidence and using quality-of-life questionnaires In addition, observing outcomes of pamidronate treatment conducted in 3-month interval	Prospective longitudinal cohort study	Components of bone changed after the antiresorptive treatment Therapy with pamidronate improved quality of life, mobility, and bone density	The direct effect of pamidronate on bone mineralization and remodeling Impacts of modern treatment and the direct effect on quality of life for children with OI
Letocha et al. (2005)	The effects of pamidronate treatment in children with types III and IV OI	18 Children with OI types III and IV (n = 18)	Nine children in the study received pamidronate (10 mg/m ² /day IV for 3 days every 3 months) Seven children in the treatment group received pamidronate for an additional 6-21 months	Randomized controlled clinical trial	Patients treated with pamidronate experienced increase in vertebral area and height Fracture rate decreased significantly in the upper extremities, but not the lower extremities Motor function, muscle strength, and pain did not change significantly throughout the trial	Effects of pamidronate on vertebral column and it relationship to pain quality in children with OI
Wiggins & Kreikemeier. (2017)	Describing the experiences of children with OI treated with bisphosphonate therapy In addition, exploring the lived experiences from the maternal perspective	6 children with OI (n = 6)	Interview and utilization of the Giorgi methodology to understand daily experiences of mothers and children through bisphosphate treatment cycles	Phenomenological study	Major themes discovered throughout interview process were living daily life in stride, normalcy is living with uncertainty, renewal with infusions, and making choices and living with the consequences	Pediatric perspective on response to treatment with bisphosphate Implications of daily living in children diagnosed with OI

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Table 1 (continued)

Author (y)	Purpose/ Research question	Sample population	Methods	Research design	Findings/Outcomes	Relevance
Franzone, Bober, Rogers, McGreal, & Kruse. (2017)	Study on intramedullary rodding of the humerus and forearm in children with OI Examining the impact on the fracture rate of those bone segments	13 Children with various forms of OI (n = 13)	The average pre-operative and post-operative fracture rates were 0.87 fractures/year (SD 0.47) and 0.10 fractures/year (SD 0.16)	Retrospective chart review	Re-alignment and rodding with intramedullary devices to reduced fracture rate of the humerus and forearm	The effect of rodding and fracture rate in the upper extremities
Suilko & Radło. (2005)	Study on how surgical treatment improved function and ambulation in children with OI	141 Children with OI (n = 141)	Intramedullary rodding procedures were performed on a large group of children with OI 321 operations were performed with each child averaging four procedures Each child had a follow up period of around 6.7 years to examine results	Longitudinal cohort study	Operative procedures were found to improve physical abilities, quality of life, and allow for an increase in activities Lower extremity rodding also helped with ambulation	Outcomes of lower extremity rodding procedures and the impact on quality of life in children with OI
Van Brussel M, et al. (2008)	Study on the direct effect on implementing an exercise program for children with OI Studying work capacity, muscle force, and subjective fatigue	34 Children with OI types I and IV (n = 34)	Children were randomly assigned to participate in 12-week exercise programs baselines were taken before, after, and 6- and 9-months following program completion	Randomized controlled clinical trial	Maximal working capacity and muscle force were significantly improved with participation in program Gains diminished after discontinuation of the program long-term	The use of exercise programs and physical therapy in the pain management of children with OI
(Santos, Pires, Soares, & Barros, 2018)	Exploring psychologically distressing situations for children with OI and their families	7 children with OI type I (n = 7)	Use of semi structured interview with open-ended questions was used to collect subjective reports of personal experience Participants included to mother, father, patient and sibling Semi-structured interviews were utilized on all 24 subjects, in addition to utilizing a retrospective chart review	Phenomenological study	Pain, fracture, and hospitalization created the most distress in children and families Comprehensive care and family involvement is important in treatment, psychological support must be provided. Four major themes 1) series of stages shaped life 2) Living with OI had ups and downs, 3) Every day normal life with OI had significant changes for parents 4) Living with OI included positive experiences Long-term intravenous bisphosphonate therapy was associated with higher lumbar spine bone mineral density and vertebral reshaping Long-term fracture rate was still high, and many participants still developed scoliosis	The role that psychological aspects play in pain response and treatment involving family dynamics and psychological counselling Understanding the psychological impact of OI on children, and coping mechanisms utilized for pain management
(Dogba et al., 2013)	A temporal analysis of the impact of severe OI of children and their families	12 Children with OI (n = 12)		Qualitative Analysis		
Palomo et al. (2015)	Examining the long-term outcomes of children with OI treated with cyclical intravenous bisphosphonate therapy	37 Children with OI type I, III, and IV (n = 37)	Reviewing data of children with OI after a 10 year follow up period that started bisphosphonate therapy before age 5 Treatment consisted of pamidronate or zoledronic acid Outcomes from other interventions such as spinal procedures were observed	Retrospective chart review		The effect of long-term bisphosphonate therapy and the role it plays on development of scoliosis Understanding pain related to lumbar spine complications in children with OI
Vanz et al. (2018)	This studied examined health related issues and quality of life of children and adolescents diagnosed with OI	52 Children with OI types I, III, and IV (n = 52)	Pediatric Quality of Life Inventory (PedsQL TM) was utilized at two reference center for treatment of OI	Prospective cross-sectional study	Physical and social functioning varied based on the severity of the OI Pain was variable and associated with deformity and fracture Pain directly affected total, physical functioning, emotional functioning, and psychosocial health	The relationship between pain and social function, physical abilities, and psychosocial wellbeing Understanding common pain responses from children with OI

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Table 1 (continued)

Author (y)	Purpose/ Research question	Sample population	Methods	Research design	Findings/Outcomes	Relevance
Kashii et al. (2019)	Determine prevalence and risk factors for the development of scoliosis in children with OI undergoing pamidronate therapy	34 Children with OI types I, III, and IV (n = 34)	Children treated with three cycles of pamidronate therapy prior to puberty. Radiographs used to examine changes in bone histology and spinal deformity	Retrospective longitudinal study	Development of scoliosis is dependent on the severity of OI and can be related to bone fragility. Lower incidence of scoliosis seen in groups that started pamidronate therapy in early childhood	The relationship between bone deformity, scoliosis, and severity of OI. The impact that bisphosphates have on development of scoliosis.
Sousa, Bompadre & White (2014)	Determine functional differences in children with mild forms of OI compared to more severe forms. Determine how bisphosphonate therapy effects functional ability and outcomes	25 children with mild and severe forms of OI (n = 25)	The Pediatric Outcomes Data Collection Instrument (PODCI) was utilized to assess function, pain and overall health status of participants	Qualitative Analysis	Children with milder forms of OI demonstrated higher functional ability and were able to participate in high level play. One year of Pamidronate therapy increased functional ability among both groups	Children with severe forms of OI have more limited functional ability than children with mild forms. Bisphosphonate therapy improves functional outcomes

OI = osteogenesis imperfecta

Table 2
Summary Table of Various Therapies for Pain Discussed in Literature Review

Total number of Articles examined in review	Number of articles discussing physical therapy	Number of articles discussing bisphosphonate therapy	Number of articles discussing surgical intervention	Number of articles discussing psychosocial support
n = 15	n = 4	n = 6	n = 4	n = 4

rate (Franzone et al., 2017). Prior to the implementation of intramedullary rodding procedures, participants in the study averaged 0.87 fractures per year, and postoperatively exhibited 0.10 fractures per year, demonstrating and overall decrease in fracture rate (Franzone et al., 2017). Data on fracture rate was generated by examining fracture in each bone segment and calculated by episodes of fracture and refracture pre- and postoperatively. Patients demonstrated an almost ten-fold reduction in fracture rate after rodding and surgical realignment of the humerus and forearm (Franzone et al., 2017). One third of patients required revisional procedures due to rod migration, common factors in patients that underwent revision were poor bone quality and severe forms of OI (Franzone et al., 2017). In a study involving 141 children with OI, intramedullary rodding procedures were performed on the lower extremities. Results indicated improvements in physical abilities, quality of life, and increased function postoperatively (Sułko & Radło, 2005).

Physical Therapy

Physical therapy is an essential component of long-term pain management in treatment of patients with OI. Physical therapists are instrumental in developing exercise programs that reduce fracture risk and bone loss, while maximizing mobility and independence (Van Brussel et al., 2008). Severity of OI must be a factor when considering participation in functional activities. In a study involving 25 children with mild to serve OI, functional ability was assessed using the Pediatric Outcome Data Collection Instrument. It was found that there is a significant difference in physical functioning between individuals with mild OI compared with counterparts with more serve forms (Sousa et al., 2014). In a study involving children with OI type I and IV, a low-resistance exercise program was implemented. Results indicated improvements in peak oxygen consumption, increased work capacity, as well as improvements in muscle strength, within three months. Improvements in these areas diminished six months after the conclusion of the pro-

gram, suggesting the need for continuous structured exercise regimens (Van Brussel et al., 2008).

In a retrospective study involving 53 children with OI, a specialized six-month exercise regimen was conducted involving whole body physiotherapy, exercise, and resistance training, as well as treadmill training (Hoyer-Kuhn et al., 2014). A six month follow up was conducted after completion of the exercise program. Results indicated an increase in motor function and walking ability (Hoyer-Kuhn et al., 2014). Total body bone mineral density also increased with significant gains in the density of the lumbar spine. Pain during exercise training was not reported in participants and fracture rate was not evaluated in this study (Hoyer-Kuhn et al., 2014).

Psychological Support

A common psychological implication of children living with OI, is a constant fear of fractures, which can impact engagement in various activities, social interaction, and influence family dynamics (Santos et al., 2018). The impact of distressing situations such as pain, hospitalization, and fractures, were examined in a phenologic study of families with children diagnosed with type I OI. It was found that psychological support is essential to treatment of children diagnosed with OI. Support can include respite care, specialized referrals, consistent communication between patients and care givers, as well as formal or informal counseling (Santos, Pires, Soares, & Barros, 2018).

A prospective cross-sectional study was conducted assessing the quality of life in 52 children with various forms of OI. The measurement of health-related quality of life was determined by using the Pediatric Quality of Life Inventory, which is an assessment instrument that uses self-report to assess physical, social, emotional, and school functioning. Multiple linear regression analysis indicated that pain directly affected overall physical and emotional function as well as psychological health (Vanz et al., 2018). Results from this study reiterated the importance of the connec-

tion between physical functioning, pain, and psychosocial health (Vanz et al., 2018). Qualitative research on the impact of severe forms of OI suggested that children with OI benefited from interaction with peers that also had the condition (Dogba et al., 2013). A small group of 12 children was interviewed. A qualitative analysis software was applied to interview responses to help develop theoretical conclusions on the impact of OI. Conclusions from his study suggested that building meaningful relationships with other individuals and families with an in-depth understanding of OI helps create a well-rounded support group, which can help children navigate throughout complex pain experiences. In addition, maintaining an optimistic viewpoint, utilizing self-acceptance, as well as adapting to physical and emotional implications of fractures, can help promote resilience and improve response to pain in daily life (Dogba et al., 2013).

Discussion

The objective of this review was to evaluate the literature on multimodal therapies and interventions that help prevent and manage pain in children with OI. To date, there is limited evidence demonstrating which intervention is ideal for pain management in children with OI. Additionally, there is lack of research regarding the long-term effects of multimodal pain management approaches in pediatric populations (Tsimicalis et al., 2018). In addition, the severity of the condition plays a quintessential role in the development of specified treatment plans for alleviating pain responses in individuals with OI. Interventions that demonstrate that increased bone stability, functionally, and bone strength are imperative measures to prevent pain. The specific etiology of pain that occurs without acute fracture is unknown, however it hypothesized that chronic pain may result from factors such as missed school days, reduced physical functioning, and psychosocial stress (Garganta et al., 2018). Avenues for improvements in psychological health must be examined to address chronic pain that may occur in the absence of fracture. Our findings from this review demonstrated goals of multimodal pain management for children with OI as promoting bone strength, increasing stability, reducing the risk of fractures and preventing further disability by maintaining muscle strength and improving psychological health.

Bisphosphonate Therapy

Bisphosphonate therapy, specifically treatment with pamidronate disodium, demonstrated benefits such as reduction in the frequency of fractures, improved bone density and clinical symptoms, as well as mobility gains (Marginean et al., 2017). Research suggests that bisphosphonates aid in the deceleration of scoliosis progression but seems to be more effective in milder forms of OI (Beary & Chines, 2019). Both oral and intravenous bisphosphonate therapy are associated with a reduction in the rate of long-bone fractures in children with milder forms of OI by 30% to 60% (Trejo & Rauch, 2016). It is unclear if intravenous and oral bisphosphonates produce the same effect on bone, specifically within the spine. Intravenous bisphosphonates have shown to improve the shape of vertebral bodies in patients with OI, while improvements in vertebral shape were not noted in similar studies involving oral bisphosphates (Trejo & Rauch, 2016).

Scoliosis development in children is affected by the subtype of OI and shares a direct relationship with bone fragility. Patients with OI type III and IV, demonstrated a higher prevalence of scoliosis. Factors such as fragility of vertebral bodies, abnormal mobility of intervertebral joints, pelvic frontal tilt, leg length disparities, and late achievement of motor milestones, could be causative factors of scoliosis in patient with OI (Kashii et al., 2019). This was also noted

by Letocha et al., (2005), in the controlled clinical trial examining pamidronate use in children with OI types III and IV. Variability in response to treatment was noted as children demonstrated decreased vertebral compression and lower rates of upper extremity fractures, however during extended treatment phases did not improve in pain response or lower extremity fracture rate. Bisphosphonate therapy alone cannot fully alleviate the pain that occurs with OI; however, it can act as an adjunct therapy in the management of the disorder by increasing bone strength, reducing fractures, and scoliosis development. This in turn can help facilitate orthopedic surgical intervention and the utilization of physical therapy (Palomo et al., 2015).

Surgical Interventions

Surgical intervention and rodding procedures are often a necessary step to improve functional ability in children with OI that experience recurrent fractures and progressive bone deformity (Franzone, Bober, Rogers, McGreal, & Kruse, 2017). Early initiation of surgical intervention not only prevents a vicious cycle of recurrent fractures, but also preserves muscle strength, prevents atrophy, and decreases length of immobilization (Bhaskar and Khurana, 2019). Intramedullary rodding has been shown to help correct deformity and reduce fracture rate, however, the complex interplay between collagen in bone and soft tissue often determine overall functional ability (Bhaskar and Khurana, 2019). Orthopedic surgical intervention can also be utilized to correct length discrepancies within the lower extremities. Variation in length of the lower extremities has been shown to be correlated with recurrent fractures, back pain, and progression of scoliosis (Marr et al., 2017). Surgical intervention is just one aspect of multimodal therapy that can help modulate pain experiences in children with OI. It is important to note that recurrent fracture and bone deformity can produce acute and chronic pain, reducing the occurrence of fracture is a key component in managing pain in this unique population. In addition, the utilization of bisphosphonate therapy in conjunction with surgical intervention is essential to maintain bone structure for successful outcomes of rod implantation procedures.

Physical Therapy

Participation in muscle strengthening activity and maintenance of joint stability through physical therapy may also help modulate pain experiences in children with OI. Regular participation in therapy can help patients preserve movement in joints and prevent muscle atrophy. Other forms of physical therapy, such as hydrotherapy, can be effective in developing strength and maintaining range of motion within joints, especially following surgical intervention (Marr et al., 2017). Hydrotherapy can be utilized in conjunction with weight bearing exercise to promote bone strengthening (Marr et al., 2017). Muscle force and bone strength share a strong association; consistent participation in structured exercise regimens may help improve subjective fatigue and well as increased exercise capacity (Van Brussel et al., 2008). Creating tailored exercise programs for children with OI may be beneficial as improvements in muscular strength may reduce the risk of acute fracture and chronic deformity.

Specialized rehabilitation approaches such as whole-body vibration therapy coupled with resistance training have shown benefits in increasing bone mineral density (Hoyer-Kuhn et al., 2014). Considerations on the severity of OI type must be made when creating exercise regimes for children. Children with severe forms OI demonstrate lower physical functioning scores at baseline compared with others with milder forms, however, data have shown significant improvements in functional outcomes and ability to

participate in high level play when treated with bisphosphonates (Sousa, Bompadre, & Klane, 2014). Utilizing multimodal therapies that directly impact the structure of bone is essential for pain management as participation in targeted regimens may improve the structure of bone, or increase muscular force, inherently reducing the risk of fracture.

Psychological Support

Psychological wellbeing can have a drastic impact on a patient's quality of life and response to pain. Chronic illnesses can be viewed as a major stressor that impacts a child's development, school performance, as well as social or familial dynamics. Understanding the impact of chronic diseases, such as OI, may help with the development of treatments that address various aspects of pain experiences (Vanz et al., 2018). Maintaining open communication with a counselor or participating in support groups can help children with OI learn to adapt to challenges of living with acute and chronic pain (Dogba et al., 2013). Utilizing psychosocial education programs to improve stress coping in families with children diagnosed with OI has been shown to be beneficial for improving emotional health and wellbeing (Bozkurt et al., 2014). Providing caregivers with tools to successfully help children adapt to challenges of living with OI can aid in addressing nonphysical aspects of pain experiences.

Limitations

Sample size and population were two major issues within studies utilized in this review. Many samples were relatively small and utilized a retrospective design, which could add to bias, or issues in measuring key statistics within the research model. In addition, many of the studies examined in this review consisted of mixed samples of children with various forms of OI ranging from type I to IV. Due to the complex genetic variation within each form of OI, outcomes and response to treatment may have varied between participants and could lead to generalizations in data analysis. In addition, there is no standardized measurement tool for pain responses in children with OI. This can also lead to generalizations as there was no definite way to gather quantitative data on many of the studies, making it a challenge to do comparative analysis on research findings. Gathering modern studies was another significant issue in this literature review. Not only was there a lack of data on pain response in children with OI, but many studies utilized in this review were longitudinal studies that had been conducted over 10 years ago.

Conclusions

OI is a complex genetic condition that requires a collaborative approach for pain management. In order create the best treatment plan for children, multiple modes of therapy must be considered. This literature review identified four multimodal treatments utilized in the pain management of children with OI. A collaborative approach for pain management is necessary to create the best treatment plan for children, which includes multiple modes of evidence-based therapy. Nonetheless, further research is needed to explore the effectiveness of new multimodal therapies for pain management in children with OI as they become available.

In addition, the severity of the condition and specificity of the gene mutation, must be recognized, because it may directly affect the response to treatment. More conclusive studies addressing acute and chronic pain management in patients with OI must be conducted. Future research on pain management in children with OI should focus on the effectiveness of a multimodal approach and

the impact of adjunctive therapies. Developing a finite understanding of the short and long-term effects of multimodal pain management can assist in engineering therapies that improve the quality of life for future children diagnosed with OI.

Implications for Nursing

Findings from this integrative literature review demonstrate how a child with OI's pain experience can be affected by fracture, psychological health, bone deformity, and muscle atrophy. Nurses can utilize this information to aid in understanding the connection between various facets that contribute to the pain experiences of children with OI. This can assist nurses in providing pertinent patient education about the utilization of multimodal pain control methods in a clinical setting. Increasing clinical knowledge can prepare nurses to implement strategies such as the coordination of social services, physical therapy, as well as community and familial involvement.

In addition, improving nursing knowledge on this topic will help nurses advocate for the integration of early surgical intervention and the use bisphosphate therapy for pain management. Encouraging surgical procedures when necessary, could improve patient outcomes by correcting bone deformities, which would decrease the incidence of chronic pain, as well as encourage independent patient ambulation. Nurses can also improve pain experiences of children with OI by advocating for increased parental involvement. Providing parental procedural education and information about maintenance and care of surgical sites, family support, and postoperative pain, can help patient's adjust after invasive surgical procedures. Educating patients and their families on the use of bisphosphates and participation in regular physical therapy will help enhance understanding of the therapeutic plan, improve adherence and ultimately, bone strength and prevent acute fracture. Lastly, nurses can apply their knowledge about secondary complications that increase pain response to help coordinate psychological support to increase patient satisfaction, coping skills, and maintain positive family dynamics of those affected by OI.

Conflict of interest

None.

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