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Master's Thesis

« Chronic Pain Management in Pediatric Patients: A Review »

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« Αντιμετώπιση Χρόνιου Πόνου σε Παιδιατρικούς Ασθενείς: Ανασκόπηση της βιβλιογραφίας».

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(*) Abbreviations/Definitions

Abbreviations:

FDA: Food and Drug Administration agency.

IBS : Irritable bowel syndrome.

Definitions:

Off-label: Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.

Abstract

(1) Background: Pain management in pediatric patients often presents a challenge to the practitioners caring for this patient population. The aim of this literature review is to research both pharmacological and non-pharmacological pain management strategies and provide a clear and concise review regarding the matter. (2) Method: A systematic review was conducted following PRISMA guidelines. Data sources included PubMed/Medline, Cochrane and Science Direct medical databases. (3) Results: A total of 39 references were deemed relevant and proper by the review of the literature. The results were presented in two parts, the first part of the review presents pharmacological treatment options for pediatric patients with chronic pain, and the second part presents non-pharmacological interventions, with a focus on complementary and alternative medicine practices. (4) Conclusion: The systematic review highlighted the need for more focus and research in the area of pediatric chronic pain management. It emphasized that a multimodal treatment approach, encompassing both pharmacological and non-pharmacological techniques, is probably the best option for most patients.

Key words: Pediatric pain management, pediatric chronic pain, pediatric pharmacology.

Περίληψη

(1) Εισαγωγή: Η διαχείριση του πόνου σε παιδιατρικούς ασθενείς συχνά παρουσιάζει προκλήσεις για τους ιατρούς που θεραπεύουν αυτόν τον πληθυσμό ασθενών. Στόχος αυτής της ανασκόπησης της βιβλιογραφίας είναι η διερεύνηση τόσο των φαρμακολογικών όσο και των μη φαρμακολογικών στρατηγικών διαχείρισης του χρόνιου πόνου για αυτόν τον πληθυσμό ασθενών και η παροχή μίας σαφούς και συνοπτικής ανασκόπησης σχετικά με το θέμα. (2) Μέθοδος: Διενεργήθηκε μια συστηματική ανασκόπηση ακολουθώντας τις κατευθυντήριες οδηγίες της PRISMA. Οι πηγές δεδομένων περιελάμβαναν τις ιατρικές βάσεις δεδομένων PubMed/Medline, Cochrane και Science Direct. (3) Αποτελέσματα: Συνολικά 39 αναφορές κρίθηκαν σχετικές και κατάλληλες από την ανασκόπηση της βιβλιογραφίας. Τα αποτελέσματα παρουσιάζονται σε δύο μέρη, το πρώτο μέρος της ανασκόπησης παρουσιάζει φαρμακολογικές θεραπείες για παιδιατρικούς ασθενείς με χρόνιο πόνο, και το δεύτερο μέρος παρουσιάζει μη φαρμακολογικές παρεμβάσεις, εστιάζοντας σε πρακτικές εναλλακτικής και συμπληρωματικής ιατρικής. (4) Συμπέρασμα: Η συστηματική ανασκόπηση επεσήμανε την ανάγκη για περισσότερη εστίαση και έρευνα στον τομέα της διαχείρισης του χρόνιου πόνου στα παιδιά. Τόνισε ότι μια πολυδιάστατη προσέγγιση θεραπείας, που περιλαμβάνει τόσο φαρμακολογικές όσο και μη φαρμακολογικές τεχνικές, είναι πιθανώς η καλύτερη επιλογή για τους περισσότερους ασθενείς.

Λέξεις κλειδιά: Αντιμετώπιση παιδιατρικού πόνου, παιδιατρικός χρόνιος πόνος, παιδιατρική φαρμακολογία.

Introduction

Chronic pain in pediatric patients is often maltreated or underdiagnosed compared to their adult counterparts. The symptom of pain in pediatric patients may be more difficult to care for due to communication barriers, especially in very young or non-verbal patients. However, contrary to prior beliefs, studies have shown that pediatric patients both recall and feel pain similarly to adults [1], thus pain in the pediatric community must be treated just as importantly.

In 2001, The American Academy of Pediatrics along with the American Pain Society provided a report to ensure suitable treatment of pediatric patients. This report proposed an interdisciplinary therapeutic approach, including pharmacologic, non-pharmacological, cognitive-behavioral, psychological and physical treatments. [2] Also, pain assessment is crucial for proper pain management, as not assessing pain properly may lead to poor treatment. This has led to the development of different pain assessment tools for pediatric patients of all age groups, in order to attempt to provide a clearer depiction of pain level intensity and type to the clinical practitioner. Equally, the lack of knowledge in areas of pediatric physiology and pharmacokinetics may have also created a dilemma for clinicians when it came to treating pediatric patients, especially when compared to their adult counterparts. Advances in medical knowledge in these areas mean more appropriate treatment approaches and plans may be created for the pediatric population. [3]

When it comes to defining pain, The International Association for the Study of Pain (IASP) defines pain as ‘An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage’. Chronic pain is defined as pain persisting or recurring for three months or longer. The ICD-11 chronic pain classification, a categorization developed by experts of IASP, describes 7 main categories of chronic pain. These include chronic primary pain, characterized by emotional distress and/or functional disability, and chronic secondary pain, which describes chronic pain as a symptom to a disease. [4]

Chronic secondary pain is divided into chronic secondary cancer-related, postsurgical/posttraumatic, musculoskeletal, visceral, neuropathic and headache/orofacial pain. In terms of pathophysiology, pain may be divided into three main categories: Nociceptive, neuropathic and nociplastic pain.

More precisely, nociceptive pain describes pain which is derived from actual tissue damage. Neuropathic pain describes the pain caused by nerve damage. Lastly, nociplastic pain describes pain due to altered nociception despite no actual evidence of tissue damage. [5] The occurrence and tenacity of chronic pain involves various hormonal and neurological pathways, which, depending on the cause, are often poorly understood. This, combined with the variability of pediatric physiology, frequently may create a challenging dilemma when it comes to understanding, assessing and treating pediatric pain. [6]

The most common chronic painful conditions in younger patients include headaches, abdominal pain and musculoskeletal pain. A systematic review of studies based on prevalence rates of chronic pain conditions in pediatric patients outlines a broad variation in the pervasiveness of pain depending on social, psychological and demographical factors. For example, the prevalence rates for headaches were 8% to 83%, for abdominal pain they were 4% to 53% and for musculoskeletal pain 4% to 40%. These statistics highlight that, like in adults, chronic pain prevalence in different demographic populations can be very diverse. [7] These statistics add to the complexity of treatment when it comes to these conditions, such as clinical practitioners may have an even harder time making the primary diagnosis.

Equally, a Canadian survey examining chronic pain in different age groups found that the prevalence of chronic pain increases with age, and that it is higher in households with a lower educational level. The prevalence of chronic pain in adolescents aged from twelve to seventeen years was 2.4% in males and 5.9% in females. [8] The prevalence of painful conditions in households with a less important educational level may also create difficulties when it comes to the patients seeking professional help and being in the position to be able to follow a treatment plan.

The early twentieth century saw important medical and public health innovations, which in turn led to an epidemiological shift when it comes to the health conditions affecting infants and children. Infectious diseases have diminished, while survival rates of severe hematologic or oncologic patients have improved. Chronic health conditions and disabilities among children and youth have steadily risen, which are conditions which are often associated with chronic pain. [9] The increasing number of patients dealing with chronic health conditions, which may often be accompanied by painful symptoms, further highlights the need for a better treatment approach when it comes to chronic pain.

Pain assessment.

Prompt assessment of pain in children is important regarding patient management, including patient distress. There are many tools which may be used in order to assess pain severity, according to developmental age.

I Self-report pain scales

Pain is a subjective predicament affected by many factors, notably by emotional distress, cultural factors, as well as previous experiences of pain. Thus, where possible, it is best that a patient can self-report pain intensity. Pain scales are a more accurate way to assess a patient rather than by relying on the experience of the physician. There are many self-report pain scales which can be used for pediatric patients, most notably the verbal Numeric Rating Scale (NRS-11), the Faces Pain Scale-Revised (FPS-R) and the color analogue scale (CAS). The NRS-11 scale ranks pain intensity from zero (no pain) to ten (worst pain ever possible) and may be used for children of six years of age or older. [10] The FPS-R uses six facial images, projecting various degrees of pain, and the child is asked to show which face it feels like. [11]



Figure 1. Faces Pain Scale-Revised [7]

The CAS asks the patient to move a slider along the length of the scale to convey how much pain they are in. [12] The above tools are more appropriate for evaluating acute and post-operative pain in patients, as their suitability for the assessment of chronic pain is undetermined. [13,14]

Moreover, one study by Tzes et al. (2013), found that while appropriate for children of older ages, convergent validity was questionable in patients under 7 years of age. [15]

Chronic pain assessment calls for a multidimensional approach with a special focus on how a patient functions in everyday life, including sleep patterns, school performance and social life. A tool which may be helpful in this context is the Patient Reported Outcome Measurement Information System's (PROMIS's), the Pediatric Pain Interference Scale (PPIS), as well as the Pediatric Pain Questionnaire (PPQ). [16]

II Observational pain measures.

The evaluation of behavioral signs such as facial expressions, crying, poor sleeping, not feeding adequately are especially important in non-verbal children. A change in vital signs may also be an indicator of pain, especially in younger children. [17] A large number of observational pain instruments are available, with the most recommended being the Neonatal Infant Pain Scale (NIPS) [18] and the FLACC scale [19], which stands for face, legs, activity, cry, consolability. Both these scales are considered to have a relatively low risk of bias.

Pediatric pharmacokinetics

The pharmacokinetic profile of a drug is determined by a number of physiological factors. The differences in physiology between pediatric and adult populations must be considered when treating these patients, as the pharmacokinetic profile of any drug may be altered. The largest difference between children and adults is observed in the neonatal period, making premature infants most susceptible to complications.

Many factors affect the absorption of any drug from the gastrointestinal tract. When it comes to orally administered drugs, three factors are most important: the pharmaceutical make-up of the drug, the physiology of the patient and the patient's gastrointestinal condition. Diet is a very important factor in terms of drug absorption and depends heavily on the age of the patient. In terms of physiology, reduced gastric acid formation is observed in pediatric populations. This affects the bioavailability of certain drugs. Most notably, increased bioavailability of more acidic drugs (i.e. penicillin) and decreased bioavailability of drugs of a higher pH (i.e. phenobarbital) is perceived. [20]

Lipophilic drugs have also altered bioavailability in pediatric populations due to reduced bile salt formation, which affects benzodiazepine bioavailability, among other drugs. Bile salt formation is reduced most considerably in the first 3 weeks of life. Bile salt formation is linked to drug solubility, thus drugs with poor solubility (e.g. hydrocortisone) may be affected during the first few weeks of life. Reduced gastric emptying and intestinal motility increases the time it takes to achieve therapeutic concentrations in infants under 3 months of age. Infants with congenital defects or surgically removed bowels are beyond the scope of this review and will not be discussed.

Intramuscular injections are usually avoided mainly due to pain, however, when necessary, water-soluble drugs are the best choice. Transrectal drug therapy is appropriate during an emergency or when intravenous administration cannot be attained. With transrectal therapy, there is the added risk that the infant may expel the drug before it is absorbed. The distribution of drugs is affected by age, mainly due to differences in body composition and plasma protein binding. Total body water is higher in younger children, thus higher doses of water-soluble drugs are required. As children grow older, lower doses are required due to a decrease in total body water percentage. Obese children are considered a special category, and usually require higher doses compared to their normal weight counterparts. [21]

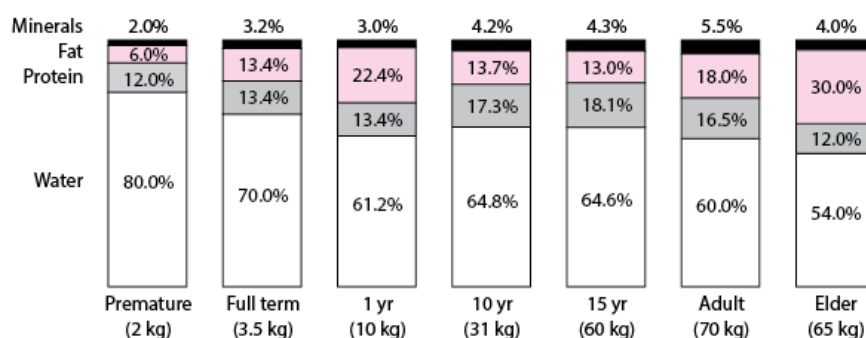


Figure 2. © Barter et al (2007): Body composition in different age groups. [21]

Protein binding is another important factor affecting drug distribution. The proteins which drugs bind to are most often: albumin and alpha-1 acid glycoprotein, as well as various lipoproteins. Protein binding affects distribution by limiting the amount of circulating free drugs. In neonates, protein concentration, most notably albumin is lower, and reaches adult level by 12 months. This results in increased free drug concentration, which means that dosage of drugs that have a high degree of protein binding should be carefully calculated in patients of this age group to avoid adverse effects.

The metabolism of drugs is also affected in pediatric populations. A study by Barter et al. (2007) states that hepatic enzyme activity is a lot lower in infants compared to adults. Due to this, for most drugs metabolism is slower in younger patients and reaches peak value at the end of the first decade of life. Interestingly, children of preschool and early school age have a high rate of drug metabolism – even higher than adults, which may be linked to higher hepatic clearance due to higher hepatic blood flow in this age group. In terms of elimination, the kidneys of neonates are generally immature, but GFR values reach those of adulthood by the first 12 months of life. Like hepatic function, kidney function also has a peak in preschool children, with the kidneys being larger in relative size at this age. [22]

To conclude, excluding the neonatal period, the pharmacokinetics differences between adults and children are not that important.

Method

Search strategy

A systematic review was conducted in order to collect relevant existing information and data related to pediatric chronic pain management. PRISMA guidelines (**P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta **A**nalysis) were followed.

The material included in this paper was carefully selected online using reliable scientific databases. References were sought using PubMed, Cochrane and Science Direct databases. After examining the types of treatment, using PICO (see below) to form a clinical question, the search strategy included the following terms: (pediatric) AND (chronic pain) AND (pharmacological) OR (non-pharmacological), (analgesics) OR (opioids) OR (neuropathic pain) OR (complementary and alternative medicine).

PICO Elements	Keywords	Search Items	Search strategies
P (Patient or Population)	Pediatric patients with chronic pain	Pediatric pain	Pediatric (AND) Chronic pain
I (Intervention)	Pharmacological and non-pharmacological	Pharmacological and non-pharmacological pain management	Pharmacological (analgesics, opioids, neuropathic pain) (OR) Non-pharmacological (complementary and alternative medicine)
C (Comparison)	Evaluation and comparison of strategies		
O (Outcome)	Effective pediatric pain management		

Table 1: PICO search strategy [23]

Selection criteria

Initially, title and abstract screening were conducted across the three online databases previously mentioned using key words relevant to the topic. Inclusion criteria encompassed: (a) patients 2 months old to 18 years old; (b) patients who had pain which was present for 3 months or more; (c) the use of both pharmacological and non-pharmacological pain management strategies, as well as complementary and alternative medicine (CAM) related references; Of the search, systematic reviews were also included and were vetted by AMSTAR-2. [24] The risk of bias in randomized controlled trials was assessed using the Cochrane RoB2 tool [25], and the risk of bias in non-randomized clinical trials was assessed by the ROBIN-I tool. [26]

Exclusion criteria encompassed: (a) references not in the English language; (b) congress abstracts; (c) studies involving only animals; (d) references where no full text was available; (e) references that were not published; (f) references that reported solely on acute pain management.

Results

The search identified 39 studies which were included in the systematic review. 9 randomized controlled trials, 9 systematic reviews, 8 retrospective studies, 6 case reports, 5 pilot studies, 1 meta-analysis and 1 open label study were selected.

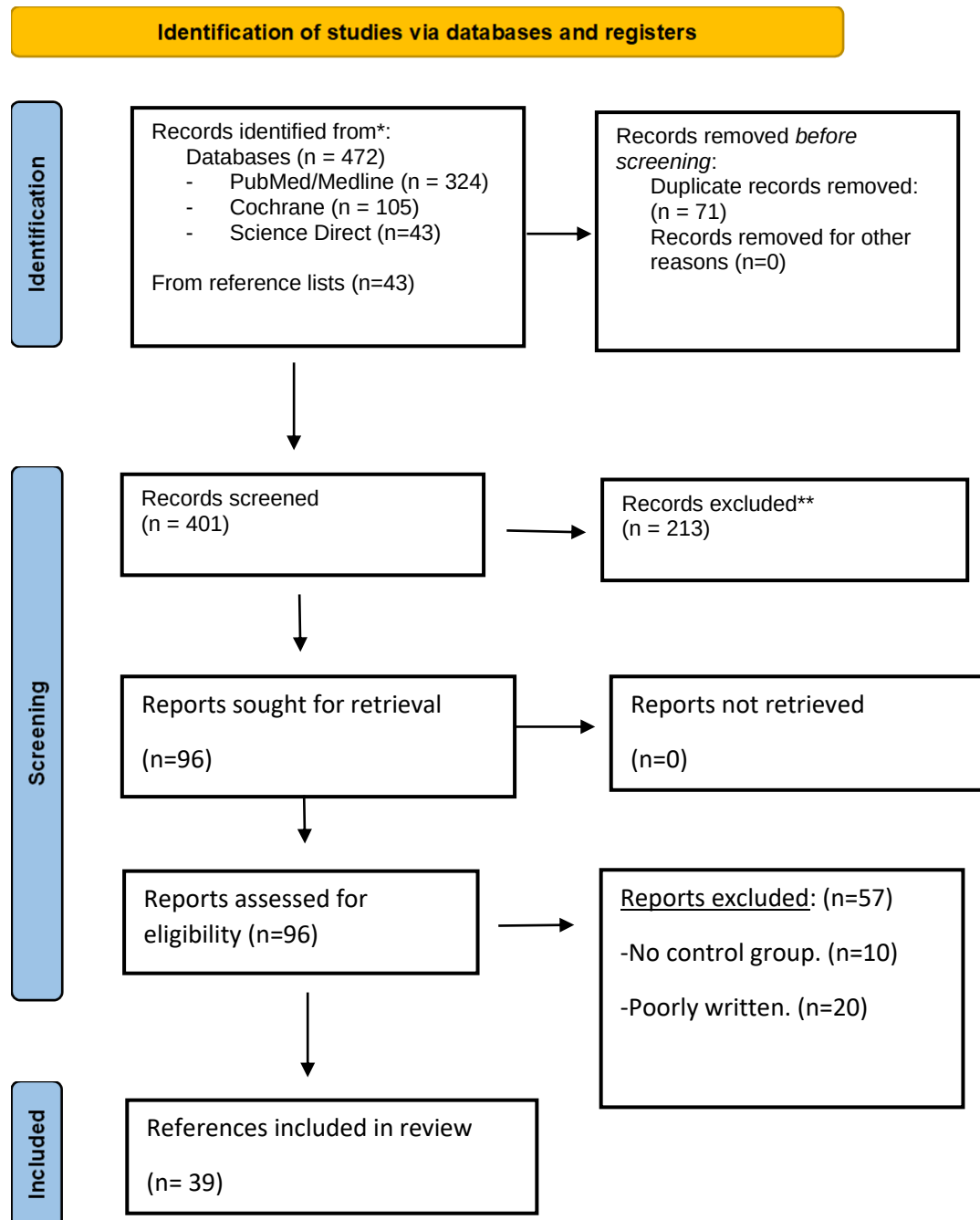


Figure 3: PRISMA flowchart for study selection. [27]

I. Pharmacological pain management

1. Traditional analgesics (Acetaminophen and NSAIDS)

Acetaminophen is one of the most widely used analgesics in children, along with non-steroidal anti-inflammatory drugs (NSAIDS). NSAIDS work by inhibiting cyclo-oxygenase (COX) enzymes and reducing inflammatory mediators in peripheral tissues. Acetaminophen, otherwise known as paracetamol, is generally a weaker analgesic than NSAIDS; however, it is often preferred due to its being very well tolerated. While its mechanism of action has been disputed, it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes. [28] These drugs are useful when it comes to the management of mild to moderate pain, while they are often included in a multimodal approach for patients requiring more severe pain management. The opioid sparing effects of acetaminophen and NSAIDS have also been well documented, especially in the perioperative period.

Six studies were identified as informative in terms of assessing efficacy and results of traditional analgesics in pediatric patients. They will be presented on the table below.

	Reference	Study Type	Results	Discussion
1.	Wong et al. (2013) [29]	Qualitative systematic review to assess opioid sparing effects of traditional analgesics.	-31 randomized controlled studies. -48 active treatment arms.	Significant opioid sparing effects in co-administration of traditional analgesics and opioids.
2.	Cooper et al. (2017) [30]	Systematic review to assess safety and efficacy of acetaminophen.	-No eligible reviews.	Inconclusive evidence to support acetaminophen use.
3.	Khairun et al. (2009) [31]	Systematic review assessing acetaminophen toxicity	-Includes 8 studies.	Pediatric patients at less risk for hepatotoxicity due to metabolic differences.
5.	Cendejas-Hernandez et al. (2022) [32]	Systematic review evaluating paracetamol safety in children.	-52 studies included.	No studies monitored neurodevelopment of children.
6.	Aleman S. et al. (2021) [33]	Meta-analysis evaluating paracetamol use during pregnancy and neurodevelopmental consequences.	-73,801 child-mother pairs across six different countries.	- 19-21 % higher chance of spectrum disorders with paracetamol use during pregnancy.

Table 2. Traditional analgesic use in children.

2. Opioids

Opioids are clinically used for their profound pain-relieving effects. In terms of classification, opioids may be divided by mode of synthesis: alkaloids – directly isolated from the flower *papaver somniferum* (examples: morphine, codeine), semi-synthetic compounds (examples: heroine, oxycodone) and synthetic compounds (examples: fentanyl, pethidine). [5] The pain-relieving benefits of opioids, as stated before, are broadly recognized, as is their high potential for dependency and abuse. Opioids act by binding to opioid receptors, which are predominantly found in the central nervous system, but also on vascular, cardiac and other tissues. Thus, opioids may be equally classified according to their effect on opioid receptors as agonists (examples: morphine, fentanyl, remifentanyl), partial agonists (examples: buprenorphine, nalbuphine) and antagonists (examples: naloxone, naltrexone). When these drugs bind to their designated receptors, this generates a series of intracellular signals, which ultimately leads to a reduction in cell excitability and neurotransmission. [34]

The selected references concerning opioid use in pediatric chronic pain management are presented below. (Table 2)

	Reference	Paper Type	Results	Conclusion
1.	Matson et al. (2019) [35]	Retrospective study.	Limited guidance on opioid use in children	Most guidelines for children are based on adult guidelines.
2.	Gmuca et al. (2018) [36]	Retrospective cohort study.	25,321 patients with chronic musculoskeletal pain.	20% of the patients were prescribed opioids.
3.	Banerjee et al. (2020) [37]	Systematic review.	(-)	Recommends restricting opioids due to adverse side effects.
4.	Lambarth et al. (2023) [38]	Retrospective cohort study.	853,625 patients	Caution repeat opioid prescriptions.

Table 3: Opioid use in chronic pediatric pain management.

3.Neuropathic Pain Options

Neuropathic pain is defined as pain caused by a disease or lesion of the somatosensory nervous system which underlies perception of touch, pressure, pain, temperature, position and vibration. [39] It may be divided into peripheral neuropathic pain (example: trigeminal neuralgia) and central neuropathic pain (example: diabetic neuropathy). [5]

	Reference	Study type	Method (or case if case report)	Conclusion
1.	McGraw et al. (1997) [40]	Case report.	Gabapentin treatment of 9-year-old patient with erythromelalgia.	Patient improvement.
2.	Phong et al. (2022) [41]	Case report	Gabapentin treatment of 7-year-old patient with erythromelalgia.	At 4 weeks patient had significant improvement.
3.	McGraw et al. (1998) [42]	Case report.	12-year-old post thoracotomy pain treated with gabapentin.	Successful treatment.
4.	Lauder et White (2005) [43]	Case series and review.	Six patients w/ cerebral palsy w/ post op neuropathic pain - treated with gabapentin.	Five out of six patients showed improvement.
5.	Low et al. (2007) [44]	Retrospective study.	20 patients w/ Complex Regional Pain Syndrome.	Patients treated with gabapentin showed positive outcomes.
6.	Akkurt et al. (2015) [45]	Case report	12-year-old patient treated with gabapentin post gunshot wound.	Showed improvement within first week-completely weaned off after two months.
7.	Behm et al. (2001) [46]	Case report.	Treatment of neonate with gabapentin.	Positive results.
8.	Edwards et al. (2016) [47]	Retrospective study	Gabapentin treatment of infants with visceral hyperalgesia.	Improved feeding tolerance, decreased irritability.
9.	Vondracek et al. (2009) [48]	Open-label study.	30 oncological patients, w/ painful peripheral neuropathy after treatment. Pregabalin 150-300mg/day (8 weeks).	86% reported significant long term pain relief.
10.	Seetharaman et al. (2021) [49]	Randomized placebo-controlled trial	Amitriptyline efficacy for functional abdominal pain disorder.	2/3 of patients showed improvement after 3-month period.
11.	Powers et al. (2017) [50]	randomized, placebo-controlled trial	Amitriptyline (1mg/kg per day) for pediatric migraine management. 132 patients in amitriptyline group.	Amitriptyline had more serious side effects compared to topiramate.

Table 4: Neuropathic pain options for pediatric chronic pain.

II. Non-pharmacological pain management

Non-pharmacological pain management strategies include pain management techniques which do not involve the use of conventional pharmaceuticals. For pediatric chronic pain patients, managing pain involves a multimodal approach involving both pharmacological and non-pharmacological methods. The goal of non-pharmacological interventions is to limit fear, distress and enhance coping strategies for the patient. Healthcare providers must also work closely with the patient's family or guardian to educate them on how to implement these techniques. This review will focus on complementary and alternative therapeutic methods for treating pediatric chronic pain.

Complementary and alternative medicine (CAM)

Complementary and alternative medicine is described as therapeutic interventions not largely used in conventional healthcare. [51] Increased reports of failed pediatric pain management have been reported, as up to 30% of patients report pain despite conventional treatment methods. [52] This statistic prompts the interest in exploring other pain management methods, to use alongside conventional treatment. CAM treatments can be divided into four categories: alternative systems, biologically based and body-based and mind-body. [53]

CAM	Therapies	Use	Age group
Alternative systems	Acupuncture	Procedural Pain	All age groups – Needle use on younger children may be difficult.
		Chronic Pain	
Biologically based	Sucrose	Procedural Pain	All age groups.
	Peppermint	Chronic Pain	
	Naturopathic herbs		
Body based	Kangaroo Care	Procedural Pain	6-18 years.
	Massage		
Mind-body	Biofeedback	Chronic Pain	6-18 years.
	Guided Imagery	Procedural Pain	
	Hypnotherapy		
	Music Therapy		
	Therapeutic Yoga		
	Meditation		

Table 5. CAM therapy categories. [53]

I. Alternative systems (Acupuncture)

Acupuncture is a needle-based treatment system which is used to treat many conditions. It is a practice grounded in traditional Chinese medicine, with principles deriving from Confucianism and Taoism. This approach presents the idea that good health comes from the alignment of vital energy, otherwise known as qi, and includes the yin/yang dualism behind its philosophy. During the treatment, an acupuncture specialist will typically use needles or other objects in order to apply pressure on certain body points, known as acupoints, to open qi, and restore wellness. It is a therapeutic option commonly used to treat chronic pain issues in adults but can be used in an array of other complications, such as in the treatment of nausea, hot flushes and tobacco cessation. Acupuncture is generally regarded as safe, as while local complications may occur at the needle site, these are usually resolved after needle removal. [54]

While the precise neurobiological mechanisms behind acupuncture have not been properly identified, it is thought that the nervous system, various neurotransmitters and several endogenous substances are associated with needle stimulation. [55] However, it must also be noted that acupuncture is also criticized by many in the scientific community and is considered to have a placebo effect on patients. [56]

Five references citing the positive results of acupuncture will be commented on.

	Reference	Study type	Patient group	Results
1.	Pintov et al. (1997) [57]	Randomized control trial.	22 patients suffering from migraines.	True acupuncture group had positive outcome.
2.	Kemper et al. (2000) [58]	Retrospective case series.	47 patients. Different conditions.	70 % of patients reported positive results.
3.	Kim et al. (2000) [59]	Randomized control trial.	Capsicum plasters on traditional acupoints.	Less pain, less opioid use.
4.	Zeltzer et al (2002) [60]	Phase I investigation study.	33 patients – different painful conditions.	6-week plan – positive outcome.
5.	Duncan et al. (2004) [61]	Randomized control trial.	50 children with spastic cerebral palsy.	96 % of patients reported improvement.

Table 3: Acupuncture in pediatric chronic pain.

II. Biologically-based therapies.

Biologically based therapies in complementary and alternative medicine use substances found in nature such as herbs, which are thought to aid as natural remedies for certain conditions.

Four references mentioning biologically-based therapies for chronic pain were included in this review. They will be presented on the table below.

	Reference	Study type	Method	Results
1.	Sarrell et al. (2001) [62]	Randomized control trial.	Herbal ear drops for otalgia vs pharmaceutical ear drops.	Both ear drops had similar effects in terms of pain management.
2.	Sarrell et al. (2003) [63]	Randomized control trial.	Similar trial to above, bigger patient group.	Similar results
3.	Weydert et al (2001) [64]	Systematic review.	Peppermint oil enteric coated capsules for recurrent abdominal pain.	Positive results.
4.	Tsao et al. (2007) [65]	Systematic review.	Sucrose on pacifier and NNS.*	Distress management.

Table 4: Biologically-based therapies in pediatric chronic pain.

* NNS : Non-nutritive sucking.

III. Body-based therapy

Body-based therapy in alternative medicine involves direct contact and/or manipulation between the carer and the patient. The patient's body is manipulated or moved in a certain way to relieve pain. Two references involving body-based therapy in pediatric patients were identified during the literature search. They are presented below.

	Reference	Study Type	Method/Patient Group	Results
1.	Tsao et al. (2007) [65] (also mentioned above)	Systematic review.	Skin on skin contact combined with NSS.	Distress management.
2.	Beider, Shay and Christopher A. Moyer (2007) [66]	Review of 24 randomized controlled Trials.	Patients between 2-19 years old.	Beneficial due to reduced anxiety and joint pain.

Table 6: Body-based therapy in pediatric chronic pain.

VI. Mind-body

Mind body therapies are holistic approaches which enhance the connection between physical and mental health and promote overall wellness. These include biofeedback, guided imagery, hypnotherapy, music therapy, yoga and meditation.

Biofeedback is a technique which is used to consciously improve the ability to alter involuntary processes. The process starts with utilizing non-invasive equipment to take measurements of a certain physical parameter. The measured parameter is then converted into a visual, auditory or tactile feedback signal. The patient then practices controlling the feedback signal by altering the physical parameter. Biofeedback techniques may be divided into two groups, either biomechanical or physiological, based on the parameter of concern in question. Biomechanical methods measure body motion using inertial sensors or in some cases, more complex video motion sensors. [67] Equally, several different techniques are used to measure physiological activity, such as electromyography to measure muscle activity, as well as heart variability to measure cardiac activity and respiratory rate to measure breathing activity. [68]

Guided imagery is a psychological intervention in which mental images are deliberately prompted to induce a relaxed state. [69] Hypnotherapy is defined as a state of induced consciousness in which a person is detached from their immediate environment and is highly responsive to suggestion. It involves focused suggestion while at the same time reduces peripheral awareness. Due to this altered state of consciousness, the patient and the hypnotherapist are thought to be able to fabricate a hypnotic reality. [70]

Music therapy is defined as the use of musical interventions to accomplish individualized goals [71] Yoga is a type of mind-body fitness, which encompasses a mixture of muscular movement and a mindful focus on self-awareness, correct breathing and energy. Yoga practicing is based on the principles that the body is a holistic entity consisting of various interconnected dimensions. This means that each dimension, or body part is connected, and that the health or ill health of one dimension affects the other. [72] Meditation is a practice involving the conscious monitoring of attention, or a concentrated focus, with the goal of calming the mind and promoting a stable state of well-being.

From the search, nine references were included in terms of mind-body therapies. They are presented on the table below (Table 5).

	Reference	Study Type	Method	Results
1.	Yetwin et al. (2022) [73]	Pilot study	Application of Heart Rate Variability (HVR) biofeedback in 21 patients aged 10-17.	Significant reductions in self-report pain scales.
2.	Yeh et al. (2019) [74]	Case study.	Biofeedback in pediatric patient with inflammatory bowel disease.	Positive results.
3.	Ostojic, Katarina et al. (2022) [75]	Crossover randomized controlled trial.	38 patients (mean age 13 years) – biofeedback vs distraction therapy for pain during botulinum neurotoxin A injections for pain management.	Biofeedback before distraction therapy yielded positive results.
4.	Folchert et al. (2021) [76]	Retrospective case series.	9 patients completed biofeedback who had persistent nonspecific wrist and forearm pain.	7 of the 9 patients had improvement of symptoms.
5.	Von Tilburg et al. (2009) [77]	Pilot study	34 patients with functional abdominal pain were divided into two groups – both were treated with standard care with one group receiving additional guided imagery.	The group who received additional guided imagery had lower pain scores.
6.	A. Offman et al. (2013) [78]	Pilot study	18 oncological patients recieved guided imagery for chronic pain.	Positive results.
7.	McGeown et al. (2015) [79]	Pilot study	29 patients underwent magnetic resonance imaging both before and after hypnosis.	Hypnosis benefits are age dependent.
8.	Caprilli et al. (2007) [80]	Pilot study.	108 patients - Music therapy for anxiety control during venipuncture compared to verbal reassurance.	The music therapy group had lower pain and stress levels.

Table 6: Mind-body therapies.

Discussion:

Pharmacological pain management

When it comes to traditional analgesics, it is clear that a combined treatment of traditional analgesics and opioids is effective at reducing opioid requirements for pediatric patients with chronic pain. From the literature search, a qualitative systematic review by Wong et al. (2013), supports this statement. This study included thirty-one randomized controlled studies and forty-eight active treatment arms (Groups receiving a specific treatment). Their findings were that twenty-one out of thirty-one randomized controlled studies (67%) and thirty eight out of forty-eight treatment arms (79%), reported a statistically important reduction in opioid requirements while co-administrating paracetamol and/or NSAIDS, for perioperative pain management in children. [29]

While paracetamol is generally considered a safe and effective drug in pediatric chronic pain management, the literature search also found that the safety and efficacy of paracetamol and NSAIDS use in chronic pain is less well documented compared to acute or perioperative pain. A study by Cooper et al. (2017) attempted to assess the safety of use of paracetamol in chronic non-cancer patients by conducting a systematic review. They concluded that no reviews were eligible to be included in their study, as the quality of evidence regarding the subject was poor. Thus, they stated that no conclusions can be made in terms of the efficacy or harm in the use of acetaminophen in the treatment of pediatric non cancer pain. [30].

In terms of long-term side effects, there has been extensive research in terms of paracetamol use and hepatic function, concluding the drug as safe for these age groups if administered in proper therapeutic doses. According to some studies, children are less at risk for hepatotoxicity due to an apparent metabolic capacity for the drug in question. [31] Interestingly, a few other factors were also mentioned by the literature as paracetamol abuse was also reported. A case report by Aneja et al. (2019) documents a 7-year-old patient with chronic pain syndrome where paracetamol abuse was observed, much like as if it were an addictive substance. The authors of this paper suggested that healthcare professionals treating young children for chronic conditions should be aware and cautious of this phenomenon. [81]

Equally, even though paracetamol is considered as a safe drug to use in early life, studies have highlighted the lack of research that has been done regarding paracetamol use and neurodevelopment. A systematic review by Cendejas-Hernandez et al. (2022) [32] explored this issue. In their review, they found 52 studies evaluating paracetamol safety in children and

highlighted that none of these studies monitored neurodevelopment. While beyond the scope of this review, a meta-analysis by Alemany et al. (2021) found that children who were exposed to paracetamol during pregnancy had a 19-21% higher chance of spectrum disorders compared to non-exposed children. [33] Therefore it may be proper to caution paracetamol use in pregnant women until further evidence is gathered on the matter.

When it comes to opioids, it is clear from the literature search that limited guidance on pediatric opioid use exists, and that most guidelines concerning opioid use in children are based on adult populations. A retrospective study by Matson et al. (2019) highlighted this issue when it comes to pediatric guidelines for chronic pain management. They also comment on how opioid abuse significantly affects adolescents, which in turn makes their use rather difficult, as well as the need for proper education on appropriate opioid usage for the families of patients, and the possibility of co-prescribing naloxone. [35]

Additionally, many opioid drugs are available commercially. However, many are not suitable for use in pediatric patients. Fentanyl, morphine and methadone are opioids which are used in patients of all ages, including neonates. For patients older than 6 months of age, oxycodone and hydromorphone are FDA* approved. Also, off-label * use of hydrocodone is common in patients younger than 2 years. Meperidine is not recommended for pediatric use due to the accumulation of its metabolite, normeperidine, that has been linked to central nervous system toxicity, including seizures. Oxymorphone is also not recommended for pediatric use, due to a higher reported risk of addiction and abuse. This is apparent especially in patients with renal dysfunction. [82] Banjeree et al. (2020) advise codeine not to be used in patients younger than twelve years of age. They also recommend avoiding codeine use in adolescents, especially in patients with respiratory problems and patients who quickly metabolize CYP2D6. [37] Equally, the FDA issued a black box warning (2017) for tramadol and codeine use in pediatric patients. In this statement, the FDA contraindicated the use of codeine and tramadol for pain management in patients under 12 years of age. They also issued a warning for tramadol in patients between 12 and 18 years of age who have other risks that may increase the respiratory depressive effects of tramadol, such as obesity or sleep apnea. These warnings were issued due to reports of difficult breathing and death. [83]

Opioids remain an important part of pain management in all age groups, including children. However, extra precautions must be taken when prescribing such drugs to these patient populations – a retrospective cohort study by Lambeth et al. (2023) found that repeat opioid

prescriptions for pediatric chronic pain management has a higher probability of leading to opioid misuse in adult years. [38] Equally, Matson et al. (2019) recommend that naloxone is co-prescribed, and that, when possible, non-opioid alternatives are preferred. [35]

Furthermore, gabapentin – originally an anticonvulsive medication – is a well-documented treatment option for neuropathic pain in adults. Most clinical investigations, concerning its efficacy in neuropathic pain in adults, examine its use in painful neuropathy related to diabetes mellitus, as well as postherpetic neuralgia [84] The use of gabapentin in the treatment of chronic neuropathic pain in children is less well documented. However, there are a few examples of its use in the literature. The first report of gabapentin use for pain management in pediatric patients dates from 1997 and concerns a nine-year-old female patient with erythromelalgia. In 1998, a twelve-year-old patient with post-thoracotomy neuropathic pain was also treated successfully with gabapentin, by the same physician [40,42]. Phong et al. (2022) also report the use of low dose gabapentin in a 7-year-old female patient with erythromelalgia, with the patient showing improvement after four weeks on a titrated regimen. [41] Its effective use in patients with cerebral palsy who developed neuropathic pain after various orthopedic procedures has been documented. Lauder et al. (2005) present six such cases, in which five of the patients showed improvement after gabapentin was included in their treatment. [43]

Additionally, Low et al. (2007) conducted a retrospective study of 20 pediatric patients with Complex Regional Pain Syndrome (CRPS), with an age range of 8-16. Eighty percent of the patients cited trauma as the cause of their illness, and the area most often affected were the lower limbs. In this case, the patients reported to have been treated with gabapentin were successfully treated and reported no side effects. [44] Another case report by Akkurt et al. (2015) examines the use of gabapentin in a twelve-year-old male patient with severe neuropathic pain after sciatic nerve damage from a gunshot wound two months earlier. The patient's rehabilitation had been compromised due to his inability to move the said limb, after a failed therapeutic attempt with NSAIDs. The patient began seeing improvements in pain levels in the first week, and by two months had been weaned off gabapentin completely. [45]

Gabapentin has also been successful in treating neonates with neuropathic pain. Edwards et al. (2016) report the use of said drug in infants with suspected visceral hyperalgesia, thought to be caused by various neurological as well as gastrointestinal morbidities.

The physicians in question reported improved feeding tolerance of said infants, as well as decreased irritability. They also reported a decreased need for other pain relief medications, such as opioids. [47]

Pregabalin - also a gabapentinoid – is thus in the same drug category as the previously discussed drug, gabapentin. The main differences between these two drugs are that pregabalin has a faster onset of action and is also more potent in a per milligram basis. The literature is not as extensive as with gabapentin. However, there are some reports of pregabalin use in neuropathic pain management in children, mainly of oncological patients. [48]

Amitriptyline, a tricyclic antidepressant, acts by inhibiting the reuptake of both serotonin and norepinephrine neurotransmitters. While it is a drug indicated to treat depression, it has a wide range of off label uses, including the treatment of chronic pain conditions, such as diabetic neuropathy and fibromyalgia. [85]

Interestingly, recent data suggests that inflammatory processes are involved in the pathogenesis of both depression and chronic pain, which may be a reason why there is a large number of patients with a co-prevalence of depression and chronic pain. [86] Despite this link, the analgesic effects of antidepressants seem to be independent from their mood-elevating effects. The analgesic effects of antidepressants seem to be mediated by the serotonergic and noradrenergic effects of the descending modulatory system, which is coordinated in the midbrain. Interestingly, while antidepressants usually take many weeks in order to relieve symptoms of depression, analgesic effects have been reported in a week. [87] Also, antidepressants with noradrenergic or mixed mechanisms of action seem to have more of a potent analgesic effect, making tricyclic antidepressants and SNRIs more effective in pain management than SSRIs. [88]

Despite its frequent use in pediatrics, there have not been many studies which examine the use of amitriptyline in chronic pediatric pain. A randomized placebo-controlled trial by Seetharaman et al. (2021) examined the efficacy of amitriptyline in functional abdominal pain disorder in pediatric patients. They found that over a three-month treatment period with amitriptyline, two-thirds of their non-placebo patient population showed improvement. [49] Other studies have been done using amitriptyline for conditions such as migraines [50]. However, as previously stated, the literature on its use in pediatric pain management is rather limited. In conclusion, more studies need to be conducted to ensure the safe use of amitriptyline in pediatric patients.

Non-pharmacological treatment options

The effectiveness of acupuncture in pediatric patients has been demonstrated in studies including children and adolescents. These studies demonstrated efficacy in a broad range of pathologies, including migraines and reflex sympathetic dystrophy. A study by Zeltzer et al. (2002) conducted a phase I investigation study examining the usefulness of acupuncture and hypnotherapy in thirty-three pediatric patients, ages 6-18 years, suffering from chronic pediatric pain. The patients had different chronic pain conditions, such as headaches, abdominal aches and complex regional pain syndrome. After a six-week treatment plan, the patients and their carers reported less pain. [60] Another retrospective case series conducted by Kemper et al. (2000) examined the effectiveness of acupuncture in 47 patients who had visited a pediatric acupuncturist. The mean age of the patients was 16 years, and a large majority (79%) were female. It was reported that 70% of patients found that the acupuncture had helped with their chronic pain. [58] The results from both these studies support the use of either acupuncture or combined hypnotherapy/acupuncture. However, it was mentioned in both these studies that further research needs to be completed in order to recommend acupuncture as a treatment option.

From the literature, one randomized controlled trial was found which examined acupuncture use for children's chronic pain. In this trial conducted by Pintov et al. (1997), the twenty-two patients complaining of migraine headaches, aged 7-15 years of age, were divided into two groups – one group was administered acupuncture, and the other was given a placebo of superficial needling. The patients, the parents or carers of the patients and the healthcare professionals administering the acupuncture or placebo were all blinded as to which group was which. In this trial, the true acupuncture group reported a reduction in symptomology, while no changes were reported in the other group. Interestingly, β -endorphin levels also rose in the true acupuncture group. This study, despite its small sample size, provides a good indicator that acupuncture can be useful in the treatment of pediatric migraines. [57]

A randomized controlled trial was also identified from the literature, using capsicum plasters on traditional acupoints, which is an alternative to traditional Chinese acupuncture. This study by Kim et al. (2006) examined its use in acute pediatric pain, specifically on 108 patients undergoing hernia repair, aged from four months to nine years of age. These patients were randomized to either receive a capsicum plaster at certain acupoints or receive a placebo tape. The capsicum plaster group showed overall less pain and less overall opioid

consumption. Although traditional acupuncture was not used, these promising results warrant further examination of employing acupuncture for pain management. [59] Generally, concerns exist when it comes to needle tolerance in younger patient populations. However, it has been reported that patients as young as one year of age have been treated successfully. In various studies, tolerance has also been demonstrated in six-year-old patients, as well as adolescents. These findings perhaps demonstrate that younger patients may not be as cautious of needles as adults would expect. [61]

The efficacy of sucrose for pain management in the neo-natal period has been examined by many studies. The sucrose is usually given on a pacifier and has been shown to be useful in distress alleviation from procedural pain, such as in cases of circumcision and venipuncture. A review of CAM by Tsao. et al. (2007) found that combined sucrose and nonnutritive sucking (pacifier use) was beneficial, which also supports the theory that nonnutritive sucking (NNS) is also a useful tactic in distress management in younger patients. [65] Another example of biologically based therapies being useful in pain management in the use of oral peppermint oil. A systematic review executed by Weydert et al. (2003) examined the various treatments for recurrent abdominal pain in pediatric patients. They found that peppermint oil enteric coated capsules were useful in managing pain in patients experiencing the gut issues mentioned. Peppermint oil has known antispasmodic properties and is considered a safe short term treatment option for various gastroenterological issues, such as IBS*. [64]

Additionally, two randomized controlled trials were identified, demonstrating the efficacy of naturopathic herbal extract in pain management. One trial by Sarrell et al. (2001) examined the use of a particular extract containing *Allium sativum*, *Verbascum thapsus*, *Calendula flores*, and *Hypericum perforatum* in olive oil. These herbs were traditionally used in ancient Chinese, Egyptian and Greco-Roman medicine and are thought to have healing properties. The patients were aged six-to-eighteen years and were experiencing otalgia due to otitis media. The patients were divided into two groups – one group received the herbal extract and another received a pharmaceutical ear drop. The study found that both solutions were equally as effective in the management of ear pain associated with otitis media.[62] Two years later, the same team conducted a similar study, but with a bigger patient population. The findings were similar to the first study, again supporting herbal extract use in the treatment of this condition. [63] While these results are promising, little research exists regarding their long-term effects of herbal supplements. Equally, herbal extracts may alter the pharmacokinetic or

pharmacodynamic properties of other medications and thus must always be prescribed with caution. [89]

In terms of body-based therapies, kangaroo care is a comforting method in which the carer holds the child skin to skin against their body at an upright angle and covers the child with a shirt. This skin-to-skin contact is thought to reduce procedural pain, especially when combined with sucrose or NNS. [90] Such remedies involving touch as a comforting mechanism are difficult to quantify scientifically. Thus, literature involving this specific pain management technique is limited.

Equally, massage therapy is thought to have many benefits on the human body, including improving circulation and promoting overall well-being. It is thought that massages activate parasympathetic pathways, reduces cortisol levels and improve sleep, among other benefits. Tsao et al. (2005) found massage therapy to be helpful in reducing pain and improving sleep, as well as mood in pediatric patients with juvenile rheumatoid arthritis, fibromyalgia, as well as certain types of cancer. [65] Beider et al. (2006) conducted a review of randomized controlled trials regarding pediatric massage and found that pediatric patients may benefit through reduced anxiety and joint pain. [66] However, research is limited, and rather minimal.

When it comes to biofeedback, it is clear from the literature that it has not been extensively examined when it comes to pediatric patients. One pilot study by Yetwin et al. (2022) examined the application of Heart Rate Variability (HRV) biofeedback in twenty-one patients aged 10-17 years. These researchers found that patients attained important reductions in self-reported pain intensity. [73] Similarly, a case study by Yeh et al. (2019) found biofeedback techniques to be helpful in a pediatric patient with inflammatory bowel disease. [74] Other studies found biofeedback to be useful in more immediate settings where pain management is needed, such as when administering botulinum toxin injections, as well as in non-specific forearm pain. [75,76]

Regarding guided imagery, several studies were identified where this type of therapy was used in the treatment of pediatric chronic pain. Van Tillburg et al. (2009) conducted a pilot study in which 34 children diagnosed with functional abdominal pain – a condition, which as previously stated, is thought to be due neuropathic pain mechanisms – were treated with standard medical care or combined guided imagery and medical care, found that the patients treated with a treatment plan that encompassed guided imagery had superior results. [77]

Furthermore, A. Offman et al. (2013) conducted a developmental and evaluation study on 18 oncological patients with chronic pain. They also found that guided imagery helped alleviate the patients' symptoms more than conventional therapy alone. [78]

Hypnotherapy is also favorable for chronic pain management. It is reported to be useful in the treatment of chronic painful conditions such as chronic migraines, irritable bowel syndrome, and pain caused by oncological treatments. [91] Interestingly, it is reported that children are more easily hypnotized than adult patients, and that they also respond excellently to hypnotherapy for acute and chronic pain conditions. It is thought that this is due to children having less defined boundaries between imagination and reality, and thus are more easily led into a trance state. According to McGewon et al (2015), in patients younger than three years of age, hypnotic ability is thought of as limited. It begins to be useful in patients who are five years old and above, and peaks at the ages of seven until fourteen. [79]

The therapeutic benefits of music for pediatric acute pain is mentioned in a number of studies. These studies include using music for procedures such as venipuncture, injection and wound dressing. The music is usually recorded lullabies, played either through headphones or on speakers. However, music therapy, a discipline in which therapists are coached to aid a patients' rehabilitation through an active musical experience, is not so well documented in the literature. One controlled study, by Caprilli et al. (2007) examined the benefits of using active music therapy to help the anxiety of children undergoing venipuncture. 108 patients were included in the study, with ages from 4-13 years, and were divided into two groups – the control group received emotional support from their parents. Lower pain and stress levels were reported in the group receiving the musical therapy. [80] From the literature, only studies documenting music therapy in acute pain management cases were identified, thus the efficiency of music therapy in chronic pediatric patients is not known.

In terms of yoga therapy, it is clear that research involving yoga and pediatric chronic pain is limited. One four-week study involving Iyengar yoga, a type of yoga which uses different props such as cushions and other materials to achieve the desired body poses, found that pediatric patients with irritable bowel syndrome, compared to a standard therapeutic control group, showed important improvement when it came to disability, coping and anxiety scoring. [92] However, since the study was home-based, it is difficult to quantify these results, as it is not possible to measure to what level the patients adhered to yoga practice.

However, yoga has known body-mind benefits and thus may be a beneficial addition to a wellness program for pediatric patients with chronic pain issues.

Lastly, it is thought that meditation helps when it comes to pain management by distraction – recognizing somatic pain and dealing with it in a calm, accepting manner. It is well accepted that mindful meditation may decrease somatic pain in adults with a variety of pain conditions, including fibromyalgia and cancer pain. [93] However, no empirical studies have been conducted regarding use of meditation in children's pain. Nevertheless, it may be helpful when dealing with older pediatric patients who will be able to conform to this sort of therapy.

Limitations

The heterogeneity in terms of the array of treatment options could be a limitation to this systematic review. Since both pharmacological and non-pharmacological treatment options were included, comparing outcomes of different treatment options could lead to confusing results. Perhaps focusing on solely pharmacological or non-pharmacological treatment options could limit this phenomenon.

Many studies which were retrieved during the review had patient populations with large age ranges. This poses a concern since different outcomes would be expected in different ages groups due to differences – primarily - in physiology. To improve the validity of this systematic review, more specific age ranges should be considered when examining the pediatric population.

In terms of complimentary and alternative medicine, the studies on mind-body and body-based therapies had comparably small sample sizes and lacked sustainable follow up, thus limiting the applicability of their outcomes for larger patient populations.

The literature search extended from 1994 until 2024, to attempt to include both new and older studies and encompass all literature on the matter. However, including older studies in the systematic review could lead to bias and non-updated information.

Conclusion

This systematic review highlights that pediatric chronic pain management is a field which requires more focus and research. It is clear that for the practicing physicians tending to this patient population, pediatric patients pose an important challenge compared to their adult counterparts. The differences in physiology which vary according to age, the inability for clear communication within this patient population and general lack of research regarding the topic make the management of pediatric painful symptoms rather complex.

When it comes to pharmacological treatments, the systematic review emphasizes the fact that most common analgesics are suitable for pediatric patients. However, it also underlined the fact that many opioids are contraindicated. Also, pediatric patients, just like their adult counterparts, are at risk for developing substance abuse. It is advised that parents and carers of patients must be vigilant when it comes to signs of abuse and it is recommended that naloxone may be co-prescribed with opioids.

In terms of complementary and alternative medicine, it is evident that practitioners remain cautious when it comes to performing or recommending these treatment options to pediatric patients compared to adults. The lack of confidence and social stigma associated with these treatments, as well as perhaps the hesitance of the parents or carers, are possibly reasons for the lack of research in this area when it comes to pediatric populations.

The systematic review italicized the fact that many treatment options are available to pediatric populations, and that a combination of different treatments, both pharmacological and non-pharmacological, seems to lead to the best outcome. However, attentiveness must be encouraged in the case of pediatric populations due to increased risk of adverse effects with conventional pharmaceutical therapy, compared to adults. Health workers must take a multidisciplinary approach when treating young patients, which must also include the education and guidance of the patient's parent or carer.

Treating pediatric patients will always come with an array of intricacies compared to the treatment of our older patients. Health practitioners should be empathetic and considerate when it comes to treating pain in these patients, as it may be just as present, and just as insufferable as in older patients.

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