Pain medication use for musculoskeletal pain among children and adolescents

a systematic review

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Systematic Review

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Abstract

Objectives: Musculoskeletal pain is common among children and adolescents. Despite the lack of evidence regarding harms and benefits, musculoskeletal pain is often managed with pain medication. The aim of this systematic review is to assess the prevalence of pain medication use for musculoskeletal pain among children and adolescents and the factors and side effects associated with use.

Content: Three databases (EMBASE, CINAHL and PsychINFO) were systematically searched to identify studies designed to examine the prevalence, frequency or factors associated with the use of pain medication for musculoskeletal pain in children and adolescents (aged 6–19 years). The included studies were assessed for study quality and data were extracted.

Summary: The search initially provided 20,135 studies. After screening titles, abstracts and full-texts, 20 studies were included. In school settings, 8–42% of children used pain medication for musculoskeletal pain, and 67–75% of children in sports clubs and from pain clinics used pain medication. The most consistent factors associated with the use of pain medications were pain characteristics and psychological factors (e.g. being bullied, low-self-esteem), while mixed evidence was found for increasing age and female gender. Only two studies reported on the duration of use and only one study on adverse effects related to the use of pain medication.

Outlook: We found that 8–42% of adolescents from school-based samples use pain medication for MSK pain, while the prevalence among adolescents from sports clubs and pain clinics is higher (67–75%). Pain characteristics (pain duration, severity, intensity, disability levels and the presence of ≥2 pain conditions or multisite pain) and psychological factors were associated with a higher use of pain medication, while for higher age and female gender the evidence of association was mixed. Future studies should systematically collect information on the type, duration of use of pain medication and side effects to confirm the findings of this review.

Keywords: adolescent; children; musculoskeletal pain; pain medication.

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Introduction

Musculoskeletal (MSK) pain is common in the general population and affects up to 40% of children and adolescents [1]. One in every two adolescents develop a MSK pain complaint that lasts for 2 weeks and between 20 and 40% of these adolescents will continue to experience recurrent pain episodes transitioning from adolescence into adulthood [2–6]. Previous research show that back and neck pain alone are the fourth leading cause for years lived with disability globally in 10–14 years old, and similarly for older (15–19) adolescents [7]. MSK pain affects the health-

related quality of life and health behaviors such as physical activity [8, 9], and is associated to anxiety, depression and sleep problems [8–11].

Data from the U.K., Australia and Spain show that annually up to 10% of adolescents have a consultation with their general practitioner due to MSK pain [12–16]. First line treatment for children and adolescents with MSK pain is often pharmacological despite there is lack of evidence to support this approach or its safety, as shown by recent reviews [17–21]. Pain medications are often easily accessible in most countries, which may drive its use. This is exemplified by the common use of pain medication for non-musculoskeletal pain conditions, such as headache, where the prevalence of use has been reported to be up to 89% in a review that included 12 studies from several countries [22]. However, the prevalence of the use of pain medication specifically for MSK pain is not known. In addition, users often lack knowledge regarding efficacy, side effects and consequences of a prolonged use [18, 22–24].

Inadequate knowledge may lead to inappropriate use of pain medication among children and adolescents [22, 25–27]. Furthermore, it remains to be investigated if inappropriate use of pain medication may contribute to long-term health-issues [19, 20]. This is important as persistent misuse during adulthood may be predicted by a behavioural pattern developed during adolescence [22, 24, 28]. This underlines the importance of investigating the prevalence of the use of pain medication for MSK pain (both prescribed and over-the-counter) in children and adolescents, and the factors and side effects associated with use. This knowledge can contribute to a broader understanding of the use of pain medication. Furthermore, it can aid healthcare professionals working with children and adolescents in guiding the rational use of pain medication for MSK pain. Therefore, the primary aim of this systematic review is to synthesize the literature investigating the prevalence of use of pain medication (i.e. paracetamol, non-steroidal antinflammatory drugs, opioids) for MSK pain among children and adolescents. The secondary aim is to assess the factors and side effects associated with the use of pain medication for MSK pain among children and adolescents.

Methods

The protocol for this systematic review was registered prior to initiation and was made publicly available in Open Science Framework (OSF) [29]. The development of the study protocol of this systematic review as well as the reporting of results followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement [30].

Literature selection

A literature search strategy was developed using a combination of medical subject headings (MeSH) and text words related to the child/adolescent (e.g. child, children, adolescent, teenagers, schoolchildren, school), MSK pain (e.g. back pain, neck pain, knee pain, chronic widespread pain), study design (e.g. prospective study, retrospective study, cross-sectional study) and pain medications (e.g. paracetamol, aspirin, opioids, NSAID, ibuprofen, codein) categories. The search strategy is outlined in Supplementary Material. Key words were identified by the senior investigator (AA) after consulting systematic reviews on the topic of MSK pain and pain medications and discussions with the other reviewers and research librarians at Aalborg University.

All databases were searched from inception to the 5th of May 2021. The EMBASE, CINAHL and PsychINFO scientific databases were searched. The search terms included in the strategy were tailored to each specific scientific database.

Eligibility criteria

Eligible studies had to report data on the outcomes of this review. The primary outcome was the prevalence of the use of pain medication for MSK pain in children and adolescents. The secondary outcomes were the factors and side effects associated with the use of pain medication for MSK pain in children and adolescents. Studies designed to investigate the 1) prevalence 2) use (e.g. doses, frequency, duration) 3) factors and side effects associated with the use of pain medication for MSK pain were included. Studies where information on the use of pain medication for MSK pain was reported in the abstract were also included. Pain medications such as paracetamol, non-steroidal antinflammatory drugs and opioids were considered. MSK pain was considered as pain arising from the components of the MSK system (muscles, joints, bones, ligaments and tendons) [31, 32]. Studies reporting on adolescents with either MSK pain of a duration <3 months or MSK pain of a duration >3 months, as defined by the International Association for the Study of Pain [33], were considered. Studies had to include children and adolescents aged 6–19 years old. According to the World Health Organization (WHO) consolidated guidelines [34], June 2013, "child" is a person 19 years or younger unless national law defines a person to be an adult at an earlier age and "adolescent" a person into the 10 to 19 age category. In addition, the age range 6–19 is chosen as the age of 6 is considered as the starting age for a child to be able to reliably self-report pain [35, 36]. Peer-reviewed studies published in English, Scandinavian languages, Spanish, Italian were eligible for inclusion. Studies published in any other language (e.g. Portoguese) that could be translated by the authors were also considered for inclusion. Studies with a prospective, retrospective or cross-sectional study design were included. Randomized controlled trials (RCTs) were excluded as an intervention was delivered and the required selection criteria would likely compromise generalizability. Studies were excluded if: data were reported on adults only, if separate information for children and adults in case of a mixed sample were not available or if children under the mean age of 6 were included in the sample. Studies were further excluded if pain medication was not used for MSK pain or if focusing on populations with specific diseases or conditions (e.g. cancer pain) where pain is assessed and reported but is a result of the disease or underlying condition. Studies reporting treatment in the acute setting (e.g. treatment for acute pain related to

injuries) were excluded. Studies were also excluded if full-text was not available or if translation was not possible. An attempt was made to obtain the full-text of the article through the interlibrary loan service when the full-text was not available.

Selection process

The process of literature selection was carried out by four authors (NAJ, AA, CG and CLS) and is summarized in the following stages: 1) Initial search of articles, upload of all references on the reference manager software (Covidence) and elimination of duplicates. This stage was performed by one author (AA) with the support of the librarians at Aalborg University Library. 2) Screening of titles and abstracts to identify articles potentially suitable for inclusion. This stage was performed by two authors (NAJ and AA). 3) Full text reading and selection of the articles that met the inclusion criteria. Four reviewers (NAJ, AA, CG and CLS, two authors for each paper) who assessed eligibility of the studies undertook this stage.

Data extraction

Data was extracted by AA, NAJ, CG and CLS. Data was extracted independently by a minimum of two authors for each study and then cross checked in order to ensure consistency in the data extraction process. In cases of disagreement, the article was discussed between two authors until agreement was reached. In case disagreement remained, a third author (MSR) would decide the outcome of the disagreement. A standardized Excel data extraction form was used during the data extraction process (Supplementary Material).

Quality assessment

The quality assessment was carried out by using a modified version of the Epidemiological Appraisal Instrument (EAI). The modified version of the EAI consisted of 31 items and is displayed in Figure 1. For each item, a response was given among the following options: Yes (2 points given), Partial (1 point given), No (0 points given), Unable to determine (0 points given) and Not applicable (0 points given). The quality score range for each study was therefore 0–62. The EAI has been appraised and shown as being an excellent tool for the assessment of observational studies, cross-sectional studies and prospective studies [37]. During the quality assessment process, each article was assessed by a minimum of two authors. In cases of disagreements the items in question were discussed between two authors. A third author (MSR) would decide on the final verdict if an agreement could not be reached.

Data synthesis

Data retrieved from studies identified were synthetized, as reported in the "results" section and discussed to reflect on the credibility and thoroughness of the results. Due to heterogeneity in terms of design and measures used in the included studies, it was not possible to conduct a meta-analysis. Therefore, a narrative synthesis was considered as the most suitable method to report the results of the review. To summarize the characteristics and outline the findings of the included studies, information was presented in the text in the following sections: "Study selection process", "Quality and characteristics of the studies", "Prevalence of the use of pain medication", "Factors associated with the use of pain medication", "Side effects", "Duration of the use of pain medication". Information was also presented in tables.

Results

Study selection process

The electronic search initially provided 20,135 studies, of which 17,694 remained after duplicate deletion. After title and abstract screening 334 studies were screened for eligibility, of which 314 were excluded because they did not meet the eligibility criteria. Finally, 20 studies met the eligibility criteria and were included. The process of selection of studies in the review is outlined following the PRISMA model, Figure 2.

Quality and characteristics of the studies

Table 1 outlines the characteristics of the included studies, which were all published in English language. The included studies were from 11 countries (seven from the USA, three from Finland, two from Greece and one from Italy, Germany, Thailand, Norway, Iceland, Spain, The Netherlands and Australia each), reporting data on a total of 629,424 participants (range 80–268,228). More than half of the studies (n=11; 55%) had a sample size >1,000 participants. The majority of studies (n=9) were carried out in the school setting, while one study was from a sport club (a youth swimming team), one study from a mixed sample of sport clubs (including several youth sports teams) and schools, two from pediatric departments, two from birth cohorts, two from pain clinics and three studies were registry-based. The registry-based studies included data from four different registries: the Tennessee Medicaid program [40], and three registries of privately insured populations: the MarketScan commercial claims database [38], the HealthCore Integrated Research Database and the Arkansas Medicaid [51]. Thirteen studies were cross-sectional, six were retrospective studies and one had a prospective study design. The majority of the studies reported on adolescents aged 15–16 years old. Further, in most studies the sample had an equal distribution of boys and girls while four studies had a higher proportion of girls than boys [38, 42, 43, 57]. One study did not report on the gender distribution [46]. Five studies (25%) reported information on the ethnicity of participants, and 10 studies (50%) reported on the participation rate (for three studies this was not applicable as they were registry-based). The

Epidemiological Appraisal Instrument (EAI)
1) Is the hypothesis/aim/objective of the study clearly described?
2) Are all the exposure variables/intervention(s) clearly described?
3) Are the main outcomes clearly described?
4) Is the study design clearly described?
5) Is the source of subject population (including sampling frame) clearly described?
6) Are the eligibility criteria for subject selection clearly described?
7) Are the participation rate(s) reported? Are ascertainments of record availability described?
8) Are the characteristics of study participants described?
9) Have the characteristics of subjects lost after entry into the study or subjects not participating from among the eligible population been described? Have the details of unavailable records been described?
10) Are the important covariates and confounders described in terms of individual variables?
11) Are the statistical methods clearly described?
12) Are the main findings of the study clearly described?
13) Does the study provide estimates of the random variability in the data for the main outcomes or exposures (i.e. confidence intervals, standard deviations)?
14) Does the study provide estimates of the statistical parameters (e.g. regression coefficients or parameter estimates such as odds ratio)?
15) Are sample size calculations performed and reported?
16) Is the participation rate adequate? Is the ascertainment of record availability adequate?
17) Are subject losses or unavailable records after entry into the study taken into account?
18) Are the exposure variables reliable?
19) Are the exposure variables valid?
20) Are the methods of assessing the exposure variables similar for each group?
21) Is exposure conducted at a time prior to the occurrence of disease or symptoms?
22) Are the main outcome measures reliable?
23) Are the main outcome measures valid?
24) Are the methods of assessing the outcome variables standard across all groups?
25) Are the observations taken over the same time for all groups?
26) Is prior history of disease and/or symptoms collected and included in the analysis?
27) Is there adequate adjustment for covariates and confounders in terms of individual variables in the analyses?
28) Are outcome data reported by levels of exposure?
29) Are the outcome/exposure data reported by subgroups of subjects?
30) Can the study results be applied to the eligible population?
31) Can the study results be applied to other relevant populations?

Figure 1: Modified version of the Epidemiological Appraisal Instrument (EAI).

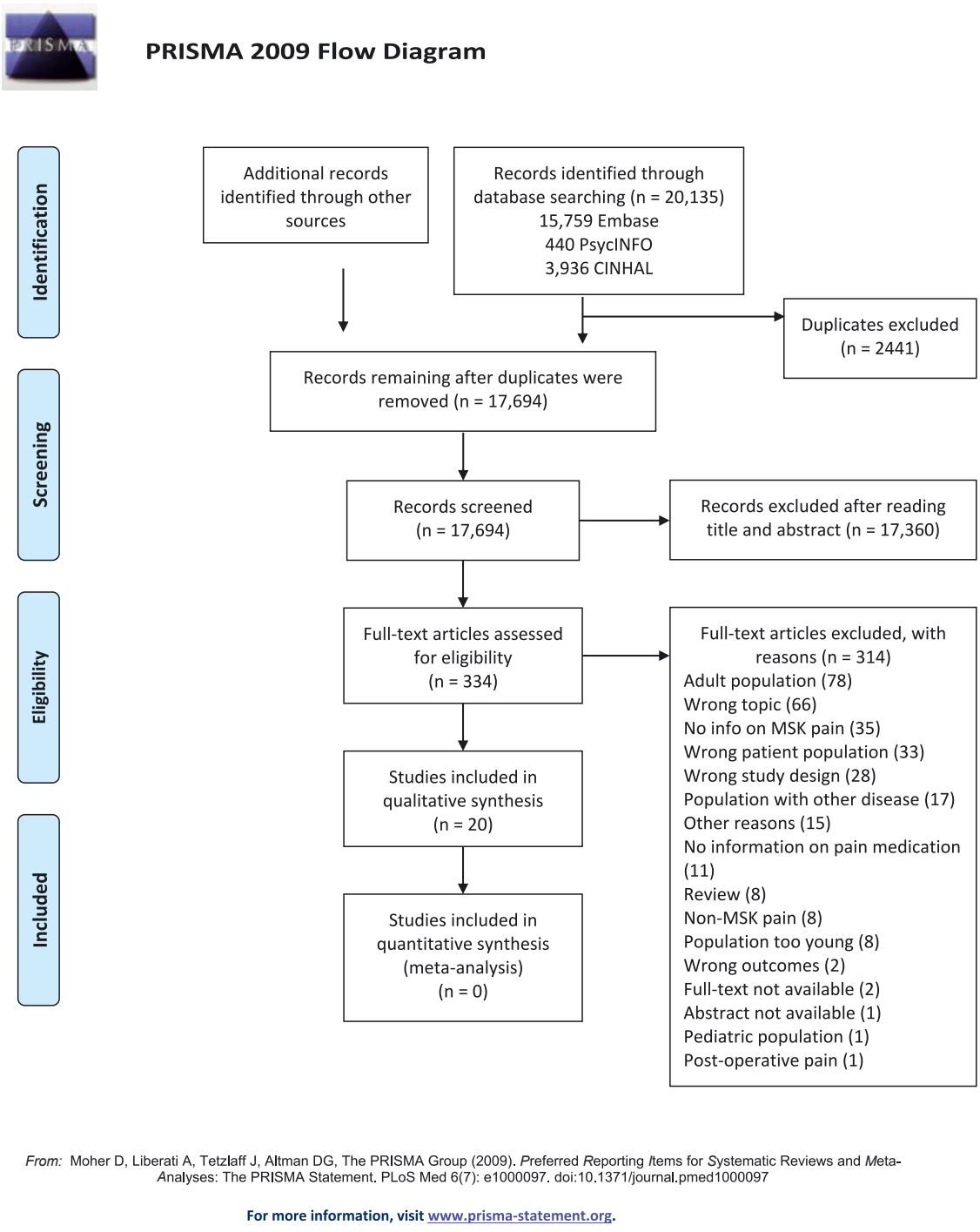

Figure 2: Flowchart showing the process of selection of the studies in the review.

studies were published between year 2000 and 2020, with the majority (15/22) published after 2010.

Based on the EAI the average quality score of studies was 36.0 (potential maximum score: 62). By applying a categorization of studies in tertiles, the scores for the studies of higher quality ranged from 39 to 47, from 31 to 38 for studies of medium quality and from 24 to 30 for studies of lower quality according to our criteria. The quality assessment for each study is outlined in Supplementary Material.

Prevalence of the use of pain medication

The prevalence of pain medication use in children and adolescents with MSK pain is reported in Table 2. Prevalence

Table 1: Characteristics of the studies included in the review.

Author (Year)	Country	Study setting	Study setting	Sample size	Mean age (range)	Gender	Participation rate	Quality score
Azad et al. 2020 [38]	U.S.A.	Retrospective	Registry-based	268,228	13.6 (5–17)	42.9% boys 57.1% girls	N/A	37
Beales et al. 2012 [39]	Australia	Cross-sectional	Birth cohort	1,391	17	47.2% boys 52.8% girls	93.4%	42
Chung et al. 2019 [40]	U.S.A.	Retrospective	Registry-based	201,940	15.2 (12–17)	44.6% boys 55.4% girls	N/A	45
Garmy et al. 2019 [41]	Iceland	Cross-sectional	School	11,018	11–15	50% boys 50% girls	84%	38
Guite et al. 2018 [42]	U.S.A.	Cross-sectional	Tertiary pain clinic	120	15.6 (11–18)	20% boys 80% girls	87%	47
Hibberd and Myers 2013 [43]	U.S.A.	Cross-sectional	Sport club	102	15.1 (13–18)	38.2% boys 61.8% girls	70%	34
Huguet and Miró 2008 [44]	Spain	Cross-sectional	School	561	11.9 (8–16)	51.7% boys 48.3% girls	62.2%	36
Iacovelli et al. 2019 [45]	Italy	Cross-sectional	School	1,301	15.9 (14–19)	47.4% boys 52.6% girls	Not reported	24
Karjalainen et al. 2013 [46]	Finland	Cross-sectional	Birth cohort	1987	16–18	Not reported	Not reported	30
Kaspiris et al. 2010 [47]	Greece	Retrospective	Pediatric department	692	11.2 (7.5–14)	49% boys 51% girls	Not reported	29
Kaspiris and Zafiropoulou 2009 [48]	Greece	Retrospective	Pediatric department	532	8.6	52.4% boys 47.6% girls	Not reported	29
Keeratisiroj and Siritaratiwat 2018 [49]	Thailand	Cross-sectional	School	2,750	10–19	50% boys 50% girls	Not reported	37
Perquin et al. 2000 [50]	The Netherlands	Cross-sectional	School	5,423	9.3 (0–18)	48.9% boys 51.1% girls	82%	44
Richardson et al. 2011 [51]	U.S.A.	Retrospective	Registry-based	HealthCore: 2001 (n=39,566), 2005 (n=64,354). Arkansas Medicaid: 2001 (n=7,384) 2005 (n=15,346)	13–17	50% boys 50% girls	N/A	27

Table 1: (continued)

Author (Year)	Country	Study setting	Study setting	Sample size	Mean age (range)	Gender	Participation rate	Quality score
Rossi et al. 2016 [52]	Finland	Cross-sectional	Sport club and schools	1,637	15.5 (14–16)	47.2% boys 52.8% girls	41%	39
Roth-Isigkeit et al. 2005 [53]	Germany	Cross-sectional	School	749	4–19	47.4% boys 52.6% girls	80.3%	43
Skaggs et al. 2006 [54]	U.S.A.	Cross-sectional	School	1,540	12.4 (10–15)	52% boys 48% girls	Not reported	35
Skarstein et al. 2014 [55]	Norway	Cross-sectional	School	367	15–16	49% boys 51% girls	59%	39
Ståhl et al. 2004 [56]	Finland	Prospective	School	366	13–16	48.4% boys 51.6% girls	71.9%	38
Tian et al. 2018 [57]	U.S.A.	Retrospective	Rheumatolo-gy clinic	80	15 (13–16)	11% boys 89% girls	Not reported	27

N/A, not applicable.

estimates varied depending on the study setting. The prevalence in an American study [57] (n=80) from a pain clinic (75%) and an American [43] (n=102) and Finnish [52] (n=1,637) study from sport clubs (62–72%) was higher compared to estimates from studies carried out in school settings (8–42%). Studies from school settings (n ranged from 366 to 11,018) were from Finland [56], Iceland [41], Thailand [49], Italy [45], Germany [53], Norway [55], Spain [44], The Netherlands [50] and the U.S.A. [54]. Among school-based studies, a low prevalence (10.4%) of pain medication use was reported in one study [45] while the remaining studies [41, 44, 49, 50, 53–56] reported prevalence estimates ranging from 15 to 42%. Studies from the pediatric department (n=532) [48] and (n=692) [47] reported a prevalence estimate between 17.5 and 23.5%. Registry-based studies (all from the U.S.A.) provided slightly different information. One study (n=201,940) [40] reported that among all the opioid prescription for several indication (i.e. dental, medical or surgical procedure, trauma, infection, headache or other pain), 5.5% of hydrocodone, 4.7% of codeine, 3.1% of oxycodone and 18.3% of tramadol prescriptions were for back or other MSK pain. The second registry-based study (2 registries included, n up to 64,354) [51], reported data on opioid prescription for chronic non-cancer pain conditions among privately insured adolescents. In 2001, 21.5–37.8% of all the prescription were for joint pain, and 21.2–39.0% for back/neck pain. In 2005, these figures increased to 21.6–41.0% (joint pain), and 21.4–44.5% (back/neck pain) [51]. Only three studies [42, 51, 57] included children and adolescents with MSK pain of a duration >3 months or with a ICD-9-CM code for MSK pain and showed the highest prevalence of use of pain medication (from 20 up to 75%). The third registry based-study [38] (n=268,228) showed that 13% of children and adolescents with low back pain were prescribed opioids within 12 months from their diagnosis.

Eleven studies reported on the type of medication used. These were mainly paracetamol and NSAIDs in studies from school settings [41, 44, 55], sport club [52] or pediatric department [47, 48]. Opioids were reported only in four American studies, one from a pain clinic [42] and three registry-based studies [38, 40, 51].

Five studies (4 from school settings and 1 from a sport club) reported on the frequency of use of pain medication. Depending on the categorization (bullied vs. non bullied), Icelandic adolescents reported using "sometimes" the following medication when experiencing pain: 40–50% paracetamol, 39–44% ibuprofen, 3–7% aspirin and 3–8% diclofenac [41]. In another study, the frequency of use of pain medication in Italian school adolescents with mild back pain was 2 times/month, while it was 5 times/month among those with moderate to severe back pain [45]. In a study among German school children who reported experiencing pain in the last three months, 39.1% reported using pain medication for their pain sometimes and 12.4% often or always [53]. In a study including Norwegian school-adolescents, 10% reported that they were daily users of over-the-counter analgesic, while 35% of them used over-the-counter analgesics less than weekly and 39% did not use them in the past previous 4 weeks [55]. In one study among 102 adolescent American swimmers, 72% reported using pain medications to manage shoulder pain, of whom 20%

Table 2: Use of pain medications in children and adolescent with MSK pain categorized by setting.

Author (Year & country)	Pain location and definition	Pain prevalence	Pain medication use %	Type of pain medication	Frequency of pain medication use
School-based studies					
Garmy et al. 2019 [41] (Iceland)	BP, NSP Definition: Pain on a weekly basis		BP 8.1% (non-bullied) 17.9% (bullied) NSP 9.3% (non-bullied) 21.5% (bullied)	Paracetamol Ibuprofen Aspirin Diclofenac	Pain medication use sometimes: Paracetamol (41.8% non-bullied; 49.1% bullied) Ibuprofen (39.4% non-bullied; 43.4% bullied) Aspirin (2.8% non-bullied; 7.2% bullied) Diclofenac (3.3% non-bullied; 8.0% bullied)
Huguet and Miró 2008 [44] (Spain)	HP, LP, ABP, CP, BP, NP, PP Definition: Troublesome pain in the last three months	HP: 43% LP: 47% ABP: 34.3% CP: 2.3% BP: 11.3% NP: 5% PP: 2.9%	42.2%	Paracetamol Ibuprofen Acetylsalicylic acid	Not reported
Iacovelli et al. 2019 [45] (Italy)	BP Definition: Pain in the last three months	87.5%	10.4%	Not reported	2 times/month (mild pain) 5 times/month (moderate/severe pain)
Keeratisiroj and Siritaratiwat 2018 [49] (Thailand)	HP, NP, SP, EP, WP, UBP, LBP, AFP Definition: Pain in the last week and in the last 12 months	76.1% (Pain in at least one area in the last week) 73.0% (Pain in at least one area in the last 12 months)	33.7%	Not reported	Not reported
Perquin et al. 2000 [50] (The Netherlands)	HP, LP, BP, EP, THP, ABP Definition: Chronic pain: pain existing for more than three months recurrently or continuously.	Chronic pain: 25% Non-chronic pain: 28% BP=4.6% LP 10.4%	39% of those with chronic pain	Not reported	Not reported
Roth-Isigkeit et al. 2005 [53] (Germany)	BP, LP Definition: Any prolonged or recurrent pain in the last three months	BP 30.2% LP 33.6%	BP 16.4% LP 22.5%	Not reported	39.1% sometimes 12.4% often or always
Skaggs et al. 2006 [54] (U.S.A.)	BP Definition: "Do you have back pain?"	37%	14%	Not reported	Not reported
Skarstein et al. 2014 [55] (Norway)	Not reported	Not reported	26%	OTC analgesics	10% daily users 35% less than weekly 39% no use in previous 4 weeks
Ståhl et al. 2004 [56] (Finland)	NP Definition: Neck pain once a month	21.3% (1-year follow-up) 43.4% (4-year follow-up)	28%	Not reported	Not reported

Table 2: (continued)

Author (Year & country)	Pain location and definition	Pain prevalence	Pain medication use %	Type of pain medication	Frequency of pain medication use
Birth cohort studies					
Beales et al. 2012 [39] (Australia)	LBP** Definition: Lifetime experience of low back pain	Cluster 1 (45.8%) Cluster 2 (63.2%) Cluster 3 (66.7%) Cluster 4 (63.9%)	Overall 16.3% Cluster 1 (13.7%) Cluster 2 (28.1%) Cluster 3 (33.3%) Cluster 4 (25.7%)	Not reported	Not reported
Karjalainen et al. 2013 [46] (Finland)	Sciatic pain Definition: Have you ever suffered from sciatic pain ever? During the past year?	Lifetime prevalence 7.2% girls 3.4% boys 12-month prevalence 6.5% girls 3.0% boys	Intensity of sciatic pain (0–3) Girls 16%, Boys 0% (4–7) Girls 52%, Boys 31% (8–10) Girls 43%, Boys 83% Physical limitations (0) – Girls 26%, Boys 9% (1–2) Girls 35%, Boys 36% (3–5) Girls 56%, Boys 60%	Not reported	Not reported
Sport clubs					
Hibberd and Myers 2013 [43] (U.S.A.)	SP Definition: Shoulder pain in the last 12 months on a scale from 0 to 10	Mild SP: 85% Moderate SP:61% Severe SP: 21%	72%	Not reported	20% 1< time/ month 33% 1–3 times/ month 47% ≥1 times/ week
Rossi et al. 2016 [52] (Finland)	LBP, NSP Definition: Pain more than once a month in the last three months	LBP girls 35% LBP boys 24.5% NSP girls 52.9% NSP boys 27.3%	67.2% sports club members 62.2% non-sport club members	NSAIDs	Not reported
Pediatric department					
Kaspiris and Zafiropoulou 2009 [48] (Greece)	GP Definition: growing pains (according to Petersen's criteria) in the last year	24.5%	17.5%	Paracetamol Acetaminophen Mefenamic acid	Not reported
Kaspiris et al. 2010 [47] (Greece)	LBP Definition: non-specific low back pain	22.1%	23.5%	Paracetamol Mefenamic acid	Not reported
Pain clinic					
Guite et al. 2018 [42] (U.S.A.)	AMPS Definition: complex regional pain syndrome, localize or diffuse musculoskeletal pain and other amplified musculoskeletal pain syndromes lasting ≥3 months	(44%) diffuse MSK pain (26%) CRPS (30%) localised MSK pain	17% Opioids 31% non-opioid analgesics	Opioids Nonopioids Psychotropic or neuropathic medications Other pain medications	Not reported
Tian et al. 2018 [57] (U.S.A.)	AMPS Definition: diagnosis of chronic musculoskeletal pain syndrome	100%	Overall 75%: 66% at least 1 NSAID, 15% at least 1 narcotic 10% at least 1 muscle relaxant 19% at least 1 antidepressant	NSAIDs narcotics muscle relaxants antidepressants	Not reported
Registry-based					
Azad et al. 2020 [38] (U.S.A.)	LBP Definition: ICD-9 code for low back pain	N/A	13.2%	Opioids	Not reported

Table 2: (continued)

Author (Year & country)	Pain location and definition	Pain prevalence	Pain medication use %	Type of pain medication	Frequency of pain medication use
Chung et al. 2019 [40] (U.S.A.)	BP, other MSK pain Definition: medical record indication for back pain or other musculoskeletal pain	N/A	5.5% of hydrocodone, 4.7% of codeine, 3.1% of oxycodone and 18.3% of tramadol prescriptions were for back or other musculoskeletal pain	Hydrocodone Codeine Oxycodone Tramadol	Not reported
Richardson et al. 2011 [51] (U.S.A.)	BP, NP, JP Definition: ICD-9-CM code for back pain, neck pain, joint pain	Health Core* JP: 81% BP/NP: 33% Arkansas Medicaid* JP: 74% BP/NP: 37%	HealthCore (2001) JP: 21.5% BP/NP: 21.2% HealthCore (2005) JP: 21.6% BP/NP: 21.4% Arkansas Medicaid (2001) JP: 37.8% BP/NP: 39.0% Arkansas Medicaid (2005) JP: 41.0% BP/NP: 44.5%	Short-acting and long-acting opioids	Not reported

BP, Back pain; LBP, Low back pain; UBP, Upper back pain; NSP, Neck/shoulder pain; HP, Head pain; NP, Neck pain; SP, Shoulder pain; EP, Elbow pain; WP, Wrist/hand pain; TP, Hip/thigh pain; KP, Knee pain; AP, Arm pain; AFP, Ankle/foot pain; ABP, Abdominal pain; CP, Chest pain; LP, Pain in the extremities/limb pain; EP, Ear pain; THP, Throat pain; PP, Pelvis pain; GP, Growing pain; AMPS, Amplified musculoskeletal pain syndrome; CRPS, Chronic regional pain syndrome; JP, Joint pain. *Prevalence estimated among all those with chronic non-cancer pain. ** Individuals were categorized in 4 clusters: Cluster 1 – Low probability of diagnosed low back pain or any other medical condition; Cluster 2 – High probability of diagnosed low back pain and neck/shoulder pain, but a low probability of other diagnosed health conditions; Cluster 3 – Moderate probability of diagnosed low back pain and high probability of diagnosed anxiety and depression; Cluster 4 – Moderate probability of diagnosed low back pain and high probability of diagnosed behavioral and attention disorders.

used them <1 time per month, 33% 1–3 times per month and 47% ≥ 1 times per week [43].

Factors associated with the use of pain medication

Fourteen studies (70%) reported information on the factors associated with the use of pain medication for MSK pain in children and adolescents (outlined in Table 3). Mixed-evidence was found regarding the association between the use of pain medication and increasing age, with four studies [38, 41, 51, 53] reporting a positive association and two studies reporting no evidence of association [44, 50]. Regarding female gender, six studies [38, 39, 44, 46, 52, 53] reported higher use in girls compared to boys and two studies [50, 55] reported a non-statistically significant association. However, it should be noted that for both age and female gender, the studies reporting no evidence of association also included the use of pain medication for non-MSK pain conditions (e.g. headache, abdominal pain) in the analysis.

Several pain characteristics were associated with the use of pain medication as assessed with a statistical test, or as shown by a marked increase in the percentage of pain medication use. These pain characteristics were: pain severity [44, 45], pain intensity [42, 46, 50, 53], pain duration [42, 44, 53], disability levels [42, 46] and the presence of ≥2 pain conditions or pain in various body sites [50, 51, 55]. Conflicting results were reported for pain frequency, which was associated with the use of pain medication in two studies [41, 56], of which one study [41] considered pain frequency as weekly symptoms of either headache, stomachache, backache, and/or neck and shoulder pain. Conversely, other studies reported that healthcare utilization [53] (e.g. visit to the doctor and/or using pain medication) or pain medication use [50] were not predicted by pain frequency. However, in these latter studies the use of pain medication might also include use for other conditions such as headache and abdominal pain, as separate analysis for each pain condition was not carried out.

Factors pertaining to the psychological domain (presence of one or more mental health condition, being bullied

Table 3: Factors associated with the use of pain medications in children and adolescent with MSK pain.

Factors associated with pain medication use	Study reporting the association	Pain location	Effect found
Increasing age	Azad et al. [38]	LBP	Patients aged 10 to 14 (OR, 2.89; 95% CI, 2.71–3.08; p<0.0001) and 15–18 years (OR, 6.98; 95% CI, 6.56–7.44; p<0.0001) were significantly more likely to be prescribed opioids Reference category: 5–9 years
	Garmy et al. [41]	BP	Increasing age associated with using analgesics during the past week OR 1.18, 95% CI 1.05–1.34
	Huguet and Miró [44]**	HP, LP, ABP, CP, BP, NP, PP	The age of the child was not related to the use of medication to get pain relief.
	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Age was not a predictor of medication use: 8–11 years (OR 0.91; 0.59–1.42) 12–15 years (OR 1.11; 0.75–1.65) Reference category: 16–18 years
	Richardson et al. [51]	BP, NP, JP	Rates of prescription were highest among older adolescents RR=1.70, CI: 1.64–1.76 (Health Core registry)* RR=1.34, CI: 1.28–1.40 (Arkansas Medicaid registry)*
	Roth-Isigkeit et al. [53]	BP, LP	The prevalence of medication use because of pain significantly increased with age (p=0.001); Healthcare utilization was predicted by increasing age (OR 1.08; 95% CI 1.01–1.16)
Female gender	Azad et al. [38]	LBP	Females were more likely than males to receive an opioid prescription (odds ratio [OR], 1.13; 95% CI, 1.10–1.15; p<0.0001).
	Beales et al. 2012 [39]	LBP	Use of pain medication by gender: 143 girls (68.4%) and 66 boys (31.6%)
	Huguet and Miró [44]**	HP, LP, ABP, CP, BP, NP, PP	Compared to boys, girls had a higher probability of having consumed pain medication (45.26 vs. 59.75%; chi-2=9.50; p=0.01)
	Karjalainen et al. [46]	Sciatic pain	Females used pain medication for sciatic pain more often than males, and the difference was statistically significant (p=0.003).
	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Sex was not a predictor of medication use: Boys (OR 0.87; 0.67–1.12) Reference category: girls
	Rossi et al. [52]	LBP, NSP	Higher use of NSAIDs in girls compared to boys among both sport clubs members (75 vs. 59.6%) and non-sport club members (73.7 vs. 46.1%)
	Roth-Isigkeit et al. [53]**	BP, LP	Girls >10 years of age used more medications for their pain than did boys of the same age (p=0.001)
	Skarstein et al. [55]		Females were not significantly more likely to be high-frequency users of OTC analgesics OR 1.89, 95% CI 0.89–4.01
Pain frequency	Garmy et al. [41]	BP	Having weekly pain was associated with using analgesics during the past week OR 7,45; 95% CI 6.32–8.78***
	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Frequency of pain was not associated with medication use: <1/month (OR 1.56; 1.13–2.15) >1/month (OR 0.86; 0.65–1.15) Reference category: >1/week
	Roth-Isigkeit et al. [53]	BP, LP	Healthcare utilization was not predicted by pain frequency (OR 0.96; 95% CI 0.85–1.09)
	Ståhl et al. [56]	NP	The proportion of painkiller users increased with the frequency of neck pain (p=0:054), from 22% (Neck pain 1 time a month) to 43% (Neck pain almost daily)
Pain severity	Iacovelli et al. [45]	BP	Increase in use of analgesic with increased pain severity (3.7% mild pain; 5.6% moderate pain; 18% severe pain).
	Huguet and Miró [44]**	HP, LP, ABP, CP, BP, NP, PP	The greater the grade of pain severity the higher the likelihood that children used medication (χ^2=25.56, p<0.01). Medication use and pain severity: Grade 0: 39.3% Grade 1: 42.3%

Table 3: (continued)

Factors associated with pain medication use	Study reporting the association	Pain location	Effect found
			Grade 2: 64.1% Grade 3: 80.0% Grade 4: 83.3%
Pain intensity	Guite et al. [42]	AMPS	Subjects who used any pain medication, compared with those who took none, reported higher levels of usual pain intensity $F[1,119]=4.55$, $p<0.05$
	Karjalainen et al. [46]	Sciatic pain	No specific analysis was performed. However, the use of pain medications increased with increasing levels of intensity of sciatic pain (especially in males)
	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Intensity of pain was positively associated with medication use <50 mm (OR 0.52; 0.40–0.67) Reference category: >50 mm
	Roth-Isigkeit et al. [53]	BP, LP	Healthcare utilization was predicted by greater intensity of pain (OR 1.30; 95% CI 1.18–1.45)
Pain duration	Guite et al. [42]	AMPS	Significant correlation found between number of pain medications used and pain duration $r=0.18$, $p<0.05$
	Huguet and Miró [44]**	HP, LP, ABP, CP, BP, NP, PP	Children with chronic pain were more likely to use medication than children without chronic pain (Chi-2=28.74; $p<0.001$, and Chi-2=12.07; $p<0.01$) Pain medication use: 54.60% in children with chronic pain 39.30% in children without chronic problems.
	Roth-Isigkeit et al. [53]	BP, LP	Healthcare utilization was predicted by longer duration of pain (OR 1,15; 95% CI 1.04–1.27)
Disability levels	Guite et al. [42]	AMPS	Subjects who used any pain medication, compared with those who took none, had higher disability scores $F[1,119]=4.15$, $p<0.05$ Significant correlation found between number of pain medications used and patient-reported disability $r=0.28$, $p<0.01$
	Karjalainen et al. [46]	Sciatic pain	No specific analysis was performed. However, the use of pain medications increased with the number of physical limitations (in both gender)
≥2 pain conditions or pain in various body sites	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Individuals who reported pain in multiple locations had used medication significantly ($p<0.001$) more often (45%) than those reporting a single pain location (33%). Single pain location (OR 1.06; 0.72–1.55) Reference category: multiple pain location
	Richardson et al. [51]	BP, NP, JP	RR=1.28, CI: 1.22–1.34 (Health Core registry)* RR=1.91, CI: 1.76–2.07 (Arkansas Medicaid registry)*
	Skarstein et al. [55]		OR 3.14, 95% CI 1.55–6.35
Pain location	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Limb pain was negatively associated with use of medication and the association was significant. Back pain was not associated with medication use Limb pain (OR 0.63; 0.48–0.84)* Back pain (OR 0.72; 0.51–1.01)
Previous prescription	Azad et al. [38]	LBP	Having a filled opioid prescription was strongly associated with a second filled opioid prescription (OR, 13.7; 95% CI, 12.9–14.5; $p<0.0001$)
Consulting a greater number of doctors	Guite et al. [42]	AMPS	Consulting a greater number of doctors for pain relief was related to use of pain medication $r=0.19$, $p<0.05$
Time to diagnosis	Tian et al. [57]	AMPS	The number of medications used (rho=–0.04; p=0.772) was not associated with time to diagnosis
Being member of a sport club	Rossi et al. [52]	LBP, NSP	Use of pain killers (NSAIDs) among sports club members (67.2%) vs. non-sport club members (62.2%), $p<0.05$; Especially in boys with LBP: sports club members (38.2%) vs. non-sport club members (20.5%), $p<0.002$

Table 3: (continued)

Factors associated with pain medication use	Study reporting the association	Pain location	Effect found
	Skarstein et al. [55]		No statistically significant differences between high and low-frequency users with regard to participation in sports
Presence of ≥1 mental health condition	Richardson et al. [51]	BP, NP, JP	RR=1.37, CI: 1.29–1.45 (Health Core registry)* RR=1.41, CI: 1.30–1.52 (Arkansas Medicaid registry)*
Being bullied	Garmy et al. [41]	BP	Being bullied at least 2–3 times monthly was associated with using analgesics during the past week OR 2.10, 95% CI 1.73–2.55
Self-esteem	Skarstein et al. [55]		Lower self-esteem was significantly associated with being a high-frequency user of OTC analgesics OR 2.77, 95% CI 1.40–5.46
Sleeping <7 h/night	Skarstein et al. [55]		Sleeping >7 h/night was significantly inversely associated with being a high-frequency user of OTC analgesics OR 0.47, 95% CI 0.24–0.91
Consumption of caffeinated drinks	Skarstein et al. [55]		Daily intake of caffeinated drinks was significantly associated with being a high-frequency user of OTC analgesics OR 2.25, 95% CI 1.14–4.45
Binge drinking	Skarstein et al. [55]		Two or more episodes of binge drinking was significantly associated with being a high-frequency user of OTC analgesics OR 3.41, 95% CI 1.76–6.62
Performing paid work	Skarstein et al. [55]		Performing paid spare-time work was significantly associated with being a high-frequency user of OTC analgesics OR 3.57, 95% CI 1.88–3.70
Socio-economic status	Skarstein et al. [55]		Good/very good perceived economic status was not significantly associated with being a high-frequency user of OTC analgesics OR 2.14, 95% CI 0.99–4.62
Parental/ethnic background	Skarstein et al. [55]		No statistically significant differences between high and low-frequency users with regard to cultural backgrounds of parents
Educational level	Perquin et al. [50]**	HP, LP, BP, EP, THP, ABP	Educational level was not associated with use of medication Lower secondary school (OR 0.87; 0.56–1.35) Middle secondary school (OR 0.62; 0.36–1.06) Higher secondary school (OR 0.76; 0.44–1.31) Reference category: Lower vocational training
	Skarstein et al. [55]		Less ambitious educational plans (ref. no plans) University OR 0.23, 95% CI 0.10–0.53 Vocational OR 0.67, 95% CI 0.27–1.65
Absence from school	Skarstein et al. [55]		Absence from school three days or more was significantly associated with being a high-frequency user of OTC analgesics OR 2.91, 95% CI 1.46–5.77

BP, Back pain; LBP, Low back pain; UBP, Upper back pain; NSP, Neck/shoulder pain; HP, Head pain; NP, Neck pain; SP, Shoulder pain; EP, Elbow pain; WP, Wrist/hand pain; TP, Hip/thigh pain; KP, Knee pain; AP, Arm pain; AFP, Ankle/foot pain; ABP, Abdominal pain; CP, Chest pain; LP, Pain in the extremities/limb pain; EP, Ear pain; THP, Throat pain; PP, Pelvis pain; GP, Growing pain; AMPS, Amplified musculoskeletal pain syndrome; CRPS, Chronic regional pain syndrome; JP, Joint pain. Healthcare utilization=visit to the doctor and/or using pain medication. *RR of being prescribed opioids, **includes medication for other pain conditions (e.g. headache, abdominal pain), ***Any weekly symptoms of pain (either headache, stomachache, backache, and/or neck and shoulder pain).

and low-self-esteem) were also associated with the use or prescription of pain medication, as reported in three different studies [41, 51, 55]. Consulting a greater number of doctors was associated with the use of pain medication in one study [42]. Regarding physical activity, being a member of a sport club was associated with the use of pain medication (especially in boys) in one study [52]. However, no differences between high and low-frequency pain medication users in relation to participation in sports were observed in another study [55]. Having an opioid prescription was associated with a future opioid prescription in one study [38] Conflicting results were found for an association between use of pain medication and educational level [50, 55]. Finally one study [55] found statistically significant associations between the use of pain medication and other factors such as sleeping <7 h per night, daily consumption of caffeinated drinks, binge drinking, performing spare-time paid work and absence from school three days or more.

Side effects

Only one study, registry based [40], reported on side effects (n=275) observed. Side effects related to the use of opioids included neurologic or respiratory symptoms (49% of cases), of which 25.8% was central nervous system depression, 3.3% respiratory depression and 30.2% neuropsychiatric symptoms. Other individuals had gastrointestinal (20.7%), dermatologic (18.5%), allergic (12.7%) or other (1.5%) symptoms [40]. However, the risk of experiencing the side effects was different depending on the type of opioid used, with tramadol and oxycodone users who had increased risk for all opioid-related side events compared to codeine and hydrocodone users. There were no studies reporting on side effects related to the use of non-opioid pain medication (paracetamol or NSAIDs).

Duration of the use of pain medication

Only two American studies (10%) [40, 51] reported on the duration of use of pain medication. In one study [40], opioids were prescribed for a mean of 4.4 days, while in another study [51] opioids were prescribed for a mean of 11.5 days in 2001 (Arkansas Medicaid registry) and 7.5 days (HealthCore registry) and 13 days (Arkansas Medicaid registry) in 2005. However, these estimates might also include the use of opioids for other non-MSK pain conditions.

Discussion

Summary

We identified 20 studies, which reported that 8–75% of children and adolescents use pain medication for MSK pain. The lowest prevalence was found in studies from school-based samples (8–42%) while 67–75% of adolescents in sports clubs or pain clinics used pain medication for their MSK pain. The most consistent factors associated with the use of pain medications were pain characteristics and psychological factors. Mixed evidence was found for increasing age and female gender, although most studies reported that these factors were associated with use of pain medication, and the studies reporting no evidence of association also included the use of pain medication for other pain conditions in the analysis.

Only two studies reported on the duration of the use of pain medication and only one study on side effects related to the use of pain medication, which assessed only opioids, however. The lack of data regarding side effects (especially related to the use of paracetamol and NSAIDs) and duration of pain medication use requires further investigation.

Comparison with previous studies and interpretation of results

We found a higher use of pain medication among children and adolescents with more severe or long-lasting MSK pain. This aligns with previous studies reporting that pain medication is the first line of treatment for chronic pediatric MSK pain [17]. Previous reviews on the use of medication in children and adolescents focused mainly on other pain conditions or symptoms (e.g. headache, allergies, fever, cold and cough, insomnia, skin problems and menstruation) [22, 23, 58], which limits comparison. These reviews report that 2–92% of children and adolescents self-medicate for these conditions [22, 58]. Importantly, these studies found that factors such as female gender, older age, maternal education and familial practices were associated with self-medication suggesting that children and adolescents with certain traits are more likely to self-medicate across different conditions [22]. This finding could be interpreted as social learning involved in self-medication as previous research have shown that mothers' use of medication was associated with their children's use [23, 59]. In our review we found mixed evidence for increasing age and female gender, although most studies reported that these factors were associated with use of pain medication, and future studies are needed to confirm this association. If evidence of association will be found, the higher use of pain medication in girls might be explained by use due to the management of menstrual pain [60]. In addition, older adolescents might tend to use pain medication independently because they want to engage in social activities despite their pain [53, 61] and, depending on the regulations on sales of pain medication of specific countries, might be able to buy pain medication themselves without the parental control [62, 63].

The higher prevalence of pain medication use found in populations regularly engaging in sport activities is in agreement with previous findings in adult athletes [64]. This could be explained by cultural factors shared by sport participants (e.g. pain medication are used to win the competition or not to lose the role in the team) [64]. This is supported by the fact that 84% of swimmers in one study [43] agreed with the statement: "Taking time off of swimming due to an injury is not a practical option if I want to succeed at a high level." [43]. Self-medication may be one of the strong drivers of the high use. The severity of self-

medication is supported by Iacovelli et al. [45] who showed that 63–80% of adolescents used analgesic for their back pain without a doctor's prescription.

Three American studies reported on opioids use in the management of MSK pain. In one study 21–44% of adolescents with joint or back/neck pain were given an opioid prescription [51], in another study 13% of adolescents with low back pain were prescribed opioids [38], while in another study 4.7–18.3% of opioid prescriptions were for back or other musculoskeletal pain [40]. This is a significant concern as opioids are currently not recommended for management of chronic MSK pain and opioid use is associated with significant risks for the patients [65, 66]. Since both studies were performed in the U.S.A., these findings may be due to cultural and healthcare system differences between the U.S.A. and most of the OECD countries (with safer opioid regulations in the European Union [67]), along with the opioid epidemic in the U.S.A. [66, 68–70].

Strengths and limitations of this study

We took several steps to ensure the quality of the present systematic review. Firstly, three different databases covering the majority of the published health-science literature were systematically searched without any time restriction and including the most common languages for publication. In addition, although it could be argued that the Pubmed or Medline databases were not searched, the EMBASE database provides the same coverage with an additional focus on drugs and pharmacology. Secondly, we focused on study designs which were compatible with the provision of information on the prevalence of use of pain medication and excluded designs which could have provided a biased estimate (i.e. RCT). Thirdly, no restriction was applied to the study settings. This enabled us to observe the prevalence of pain medication use in a broad setting and among populations with different grades of MSK pain severity (e.g. schools vs. pain clinics) or which might be more likely to experience MSK pain due to overuse (e.g. sport clubs). Fourthly, the inclusion of studies from different countries and continents allowed us to obtain an understanding on differences in use of pain medication (and type) for MSK pain. The use of pain medication may be influenced by cultural factors (pain perception and reporting as well as the prescription of pain medication varies across countries and ethnicities [71–73]) and legislations applied in the specific countries (especially regarding the availability of over-the-counter and opioid pain medication) [67]. Lastly, the majority of studies included had a high number of participants or a response rate >70%, which supports generalizability of results.

This review also presents some limitations. Different methods were used for the assessment of MSK pain (e.g. intervals considered for the prevalence, frequency, duration of pain), of pain medication (e.g. prevalence, type, frequency) and the recall period considered between studies. Therefore, recall bias cannot be excluded [74]. This may also limit comparability of the results between studies. Due to the variability in how MSK pain was measured and lack of information on pain medication we could not perform a meta-analysis to create a pooled estimate. The variability in data collection in the original studies also prevented us from subgroup analysis to explore the association between duration of pain and use of pain medication. This review focused on studies reporting on the prevalence of pain medication use among children and adolescents with MSK pain as a primary aim of the study or that reported this information in the abstract. Therefore, it is possible that other studies that did not focus on pain medication as a primary outcome but reported such information in the text or tables were not included. However, it is likely that such studies would report a lower quality information on pain medication use as this was not the main objective of those studies.

Implication for future research

This review showed that pain medication is commonly used in children and adolescents to manage MSK pain (not related to injuries, as studies reporting on acute pain resulting from injuries were not included). However, we found a lack of information on the duration of use and the side effects of pain medication, especially regarding paracetamol and NSAIDs. Future studies should strive to collect detailed information on the use which will allow to differentiate between occasional use of pain medication for MSK pain of shorter duration, which might be safe, and regular and long-lasting use that might occur for MSK pain of a longer duration. Regular and long-lasting use of pain medication might result in side effects, as it has been shown in adults [75], but there is little information available from the best evidence in children and adolescents [17–21]. Therefore, future dependencies, overuse, misuse and potential health hazardous consequences of the use of pain medication in children and adolescents should be investigated and collected. Other information that should be collected in future studies include the use of medication for concurrent comorbidities (e.g. headache, menstrual pain) and the gateway to pain medication (e.g. sport coach, family, friends, general practitioner) [22, 76, 77]. Future studies should validate which factors are associated with the use of

pain medication (e.g. bullying, being a member of a sport club, self-esteem). This might lead to the assessment and targeting of specific factors (e.g. psychological factors), which might be currently overlooked in daily practice.

Conclusions

This systematic review showed that 8–42% of adolescents from school-based samples use pain medication for MSK pain, while the prevalence in sports clubs and pain clinics is higher (67–75%). Pain characteristics (pain duration, severity, intensity, disability levels and the presence of ≥2 pain conditions or multisite pain) and psychological factors were associated with a higher use of pain medication, and mixed evidence was found for higher age and female gender. Future studies should collect information on the type, duration of use of pain medication and side effects to confirm the findings of this review.

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