TITLE PAGE

"The research gap in chronic paediatric pain:

A systematic review of randomised controlled trials"

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Conflicts of Interest

None declared.

ABSTRACT

Background and Objective Chronic pain is associated with significant functional and social impairment. The objective of this review was to assess the characteristics and quality of randomized controlled trials (RCTs) evaluating pain management interventions in children and adolescents with chronic pain.

Methods We performed a systematic search of PubMed, Embase and the Cochrane Library up to July 2017. We included RCTs that involved children and adolescents (3 months-18 years) and evaluated the use of pharmacological or non-pharmacological intervention(s) in the context of pain persisting or re-occurring for more than 3 months. Methodological quality was evaluated using the Cochrane Risk of Bias (ROB) Tool.

Results A total of 58 RCTs were identified and numbers steadily increased over time. The majority were conducted in single hospital institutions, with no information on study funding. Median sample size was 47.5 participants (Q1,Q3: 32, 70). Forty-five percent of RCTs included both adults and children and the median of the mean ages at inclusion was 12.9 years (Q1,Q3: 11, 15). Testing of non-pharmacological interventions was predominant and only 5 RCTs evaluated analgesics or co-analgesics. Abdominal pain, headache/migraine and musculoskeletal pain were the most common types of chronic pain among participants. Methodological quality was poor with 90% of RCTs presenting a high or unclear ROB.

Conclusions Evaluation of analgesics targeting chronic pain relief in children and adolescents through RCTs is marginal. Infants and children with long-lasting painful conditions are insufficiently represented in RCTs. We discuss possible research constraints and challenges as well as methodologies to circumvent them.

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Significance

There is a substantial research gap regarding analgesic interventions for children and adolescents with chronic pain. Most clinical trials in the field focus on the evaluation of non-pharmacological interventions and are of low methodological quality. There is also a specific lack of trials involving infants and children and adolescents with long-lasting diseases.

TEXT

INTRODUCTION

Chronic pain is a complex, multidimensional experience that is generally defined as pain lasting more than 3 months (Merskey and Bogduk 1994). Although, the condition is more prevalent in adults, epidemiological studies have shown that as much as 25% of children and adolescents have experienced at least once recurrent or persistent pain (King et al., 2011; Perquin et al., 2000). Migraine or functional abdominal pain account for the majority of painful experiences but chronic long-lasting conditions such as cancer or neurodegenerative conditions may also cause significant chronic pain (Hagen et al., 2008; Palermo 2009).

Experiencing chronic pain clearly has a negative impact on patients' and relatives' quality of life (Hunfeld et al., 2001; Palermo and Eccleston 2009). In children, psychomotor development and social behaviour are severely impaired leading to psychological distress, physical disability and school failure (Coffelt et al., 2013; Eccleston et al., 2006; Petersen et al., 2009; World Health Organization 2012). High levels of anxiety and depression in childhood are major risk factors for developing psychological pathologies in adulthood (Fearon and Hotopf 2001; Reinherz et al., 2003). Direct (use of health care) and indirect (e.g. parents' work loss) costs are also particularly increased in the context of paediatric chronic pain (Groenewald et al., 2014).

All of these reasons pledge for an early and efficient treatment of chronically painful conditions in children and adolescents. Current therapeutic approaches recognize the value of a multimodal treatment framework, combining use of analgesics with physical, behavioral and psychological therapies (Odell and Logan 2013). However, the analysis of the only systematic review aiming to evaluate the effects of intensive interdisciplinary pain treatment in children and adolescents with chronic pain was hampered by the non-randomised nature of the studies,

their small number and their methodological weaknesses (Hechler et al., 2015). As medical practice should be optimally driven by adequate research quality, it is important to evaluate the research available to support chronic pain management. The aim of this review was to assess the characteristics and the methodological quality of randomized controlled trials (RCTs) evaluating pharmacological and/or non-pharmacological intervention(s) for the management of persistent or recurrent chronic pain in children and adolescents.

METHODS

Electronic search query

Relevant RCTs were identified through electronic literature searches using the following databases: MEDLINE, EMBASE and the COCHRANE Library (CENTRAL and Cochrane Database of Systematic Reviews), all from inception to July 17, 2017. The following abbreviated search strategy was used: “persistent pain”, “recurrent pain”, “continuous pain”, “chronic pain”, “analgesia”, “analgesics”, “children”, “paediatric”, “adolescent”, “teenagers”, “clinical trials” and other synonyms of these terms combined by the operators Boolean (AND, OR, NOT). The exact research strategies for all electronic databases are given in **Appendix S3**. The search was done without any language restriction or date limits. Lists of references of identified studies, systematic reviews and meta-analyses were further screened for relevant articles.

Studies were eligible if (i) they were RCTs defined as any prospective study where participants were randomly allocated to study groups, (ii) included infants, children and adolescents (3 months to less than 18 years of age) and (iii) their main objective was to evaluate the effects of pharmacological and/or non-pharmacological intervention(s) for the management of chronic pain. Chronic pain was defined as pain that persisted or re-occurred in a 3 month time-period (Treede et al., 2015). Pain assessment was either the primary or the

secondary study outcome. Trials including both children and adults were also considered. Abstracts, letters, duplicates, preliminary publications and reviews were excluded. RCTs published in languages other than French or English were secondarily excluded.

Retrieved articles were assessed by two independent authors (AY, RB), who read the titles and abstracts to identify the relevant trials. Each author independently selected the trials to be included in this review. Disagreements were resolved by discussion with a third researcher (FK). For all abstracts considered potentially relevant, full texts were retrieved. Full text article selection was independently performed by three authors (AY, RB, ED) and disagreements were resolved by consensus.

Data extraction

Data were extracted using a structured data collection form (**Appendix S1**) which was pre-tested on ten randomly selected articles by one researcher (MM) and modified accordingly. The form covered the following categories: general characteristics (e.g. study setting, year of publication, funding), study population (e.g. age groups: infants [3 to 23 months], children [2 to 11 years], adolescents [12 to 17 years], adults [≥18 years]; size), clinical context (e.g. type and source of pain, presence of an underlying disease), trial design (e.g. nature of intervention and comparator, outcome measures, pain assessment, statistical conclusions) and methodological quality.

Methodological quality assessment

Methodological quality was assessed using the Cochrane Risk of Bias (ROB) Tool implemented based on the guidelines of the Cochrane Collaboration (Higgins et al., 2011). The tool covers six methodological areas: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

For each study, ROB is described as low (all six domains are judged to be at low ROB) or high (one or more domains are judged to be at high ROB) or unclear (one or more domains are judged to be at unclear ROB and none at high risk). Two authors (AY, EB) assessed methodological quality independently and discrepancies were solved by consensus.

Data analysis

We computed medians (first and third quartiles; Q1, Q3) for continuous variables and the number (percentages) for categorical variables. Analysis was performed using SAS software version 9.3 (SAS Inc, Cary, North Carolina, USA).

RESULTS

Electronic search yielded a total of 936 articles. Altogether, 40 RCTs were selected for analysis together with 18 RCTs identified through manual reference search (**Figure 1**; **list of** selected articles is given in **Appendix S2**).

General trial characteristics and study population

Table 1 summarizes the main trial characteristics and **Figure 2** displays the number of RCTs per year of publication and type of intervention evaluated. Most of the RCTs were single-center, hospital-based trials from Europe or Northern America and were recently published (after year 2005: 36/58 62%). Public funding prevailed although the information was lacking in more than half of the RCTs. Median sample size was 47.5 participants (Q1,Q3: 32, 70). Only 32 (55%) trials were exclusively pediatric (children and/or adolescents) and the median of the mean ages at inclusion was 12.9 years (Q1,Q3: 11, 15), and none included infants. The majority of RCTs (81%) evaluated the impact of a non-pharmacological intervention.

Clinical context

Participants presented a chronic pain which was persistent in 1 RCTs (2%), recurrent in 26 (45%), both in 11 (19%) but the type of chronic pain was not specified in 20 RCTs. Participants presented an underlying disease in 9 RCTs (16%). Only 29% (17/58) of RCTs specified the physio-pathological type of pain to be treated although most patients presented with more than one type of pain: nociceptive pain in 10, neuropathic pain in 8, psychogenic pain in 6 and mixed pain in 6 RCTs. Pain locations/causes are given in **Table 2** according to type of intervention. The majority of studies focused on the management of abdominal pain (64%) and headache/migraine (47%) however, 23 (40%) trials included patients with pain originating from more than one location/cause. Of note, RCTs on the management of cancer, myofascial, eye and psychosomatic pain included both children and adults.

Trial design

All RCTs aimed to evaluate the efficacy of a pain management intervention and the majority were parallel-group superiority trials (n=52; 90 %). Number of arms was 2 in 47 RCTs (81%), 3 in 9 RCTs (16%) and more than 3 in 2 RCTs (3%). Median duration of study was 28.5 (Q1,Q3: 21, 50) months and median individual participation was 6 months (Q1,Q3: 3, 12), respectively. **Table 3** summarizes the characteristics of the RCTs' outcome measures. Assessment of pain was the primary outcome in 86% (50/58) of RCTs (single assessment [n=12] or part of a composite outcome [n=38]), and a secondary outcome in 8% (n=8). Self-assessment of pain was privileged (95% of RCTs) and the numerical rating scale (NRS-11, 50%) was the most frequently used pain scale. Other important outcomes measures such as quality of life and pain-related disability were more rarely assessed (**Table 3**).

A baseline period of pain assessment before randomization was required in 83 % (48/58) of RCTs. However, the duration of this assessment period was reported only in 67% (32/48) of these trials and varied between 1 day and 6 months (median: 14.5 days). Also, a treatment

’wash-out’ period was required in 1 pharmacological RCT (7 day duration), not required in 13 (20%) and not reported in 44 RCTs (78%).

Among the 11 RCTs evaluating pharmacological interventions, 5 evaluated the use of diclofenac or nefopam, acetaminophen-codeine with or without doxylamine, amitriptylin with or without pindolol, chlormezanone and drotaverine hydrochloride respectively; the remaining trials evaluated the effects of antibiotics (n=3) or combinations of vitamins (n=3) to treat chronic painful symptoms. Overall, control groups comprised a placebo (n=5) or an active reference treatment (n=6). Of note, only 4 out of these 11 RCTs were exclusively pediatric.

For RCTs evaluating non-pharmacological interventions (n=47): 39 evaluated the efficacy of a single intervention, (psychotherapy, n=13; complementary therapy [e.g. hypnotherapy], n=5; educational approaches, n=2; surgery, n=1 and other interventions, n=13 [e.g. exercise rehabilitation program] and 7 evaluated the effects of multiple interventions. Control groups were no intervention**,** n=15; standard medical care, n=12; educational approaches, n=7; placebo, n=3; pharmacological treatment, n=1 and other (e.g. surgery or dietary therapy), n=9.

Methodological quality assessment

Among the twenty-six RCTs conducted with a blinded assessment of intervention efficacy, ten were conducted in a double-blind and sixteen in a single-blind approach. Among the 58 RCTs, only 30/58 (52%) defined the exact methods of randomization and 19/30 (63%) used computer random number generator. The allocation method was detailed only in fourteen RCTs (24%). Sealed envelope techniques were more often used as method of treatment arm allocation (9/14; 64 %).

Only 6 RCTs (10%) presented a low ROB (high ROB, n=14; unclear ROB, n=38) and they were all published after year 2005 (data not shown). However, ROB varied with the type of intervention tested. Among RCTs testing pharmacological interventions, more than half

applied adequate methods of blinding of outcome assessment, blinding of participants and personnel and reported complete outcome data (**Figure 3**). For non-pharmacological interventions, blinding of participants and personnel, reporting of complete outcome data and blinding of outcome assessment were inadequate or not described in more than half of the RCTs (**Figure 3)**. Also, RCTs involving both children and adults presented a lower risk of bias (4/26; 15%) than exclusively pediatric RCTs (2/32; 6%). Only 23/58 (40%) RCTs reported a sample size calculation and the majority (46/58) presented statistically significant results.

DISCUSSION

This is the first review to describe the current research on pharmacological and non-pharmacological pain management interventions in children and adolescents with chronic pain. Overall, few RCTs have been published, mainly single-institution, publicly funded trials of limited size. Only 55% were exclusively paediatric and none involved children of less than 2 years of age. The majority focused on the evaluation of non-pharmacological interventions in children presenting with headache/migraine or abdominal pain. Methodological quality was poor, most probably related to the absence of adequate reporting of study features.

Chronic pain is acknowledged as a growing problem with significant individual and societal repercussions that requires adequate and often multidisciplinary treatment approaches (Hechler et al., 2015). Still, this complex health problem lacks consensus on clinical definitions, severity scaling and intervention outcomes of interest even in adult medicine (Bouhassira and Attal 2011; Moore et al., 2013b; Treede et al., 2008). The absence of diagnostic tools and the difficulties in classifying chronic pain was reflected by the fact that one third of RCTs did not provide information about the physio-pathological type of participants' chronic pain. This may also be the reason why no RCT involved infants less than

2 years of age. Although pain perception and its negative effects have been clearly identified in infants as young as preterm neonates (Allegaert et al., 2013), recent experimental studies advocate that neuropathic chronic pain is suppressed in the youngest and may emerge later in adolescence (Fitzgerald and McKelvey 2016; McKelvey et al., 2015). But how can we clinically confirm the absence of persistent pain in infants who are unable to verbalise pain or discomfort and without adequate tools to recognize it? Yet, the challenge of identifying and quantifying ongoing pain is not specific to the youngest as pain intensity scales used in children and adolescents have been essentially developed to evaluate acute or procedural pain (Hummel and van Dijk 2006; Palermo 2009; Stinson et al., 2006; von Baeyer and Spagrud 2007). Though, it is recommended to use the same scales for chronic pain, there is no evidence on their psychometric properties in this clinical context (McGrath et al., 2008).

A variety of psychological therapies have proven to be beneficial for children and adolescents with persistent pain (Eccleston et al., 2012) although, one cannot refute the necessity of pharmacological treatments and the positive interactions between the two therapeutic approaches. Still, evaluation of analgesics for the treatment of chronic pain in children was very scarce. In addition, RCTs focused mainly on two causes of pain: headache/migraine and abdominal pain, while neglecting children and adolescents with long-lasting conditions causing substantial pain e.g. cancer or sickle cell disease. Both findings underline the fact that for some clinical conditions, pain therapy remains empirical and mainly based on extrapolation of therapeutic schemas from adults (Gregoire and Finley 2013; Mercadante and Giarratano 2014).

Clinical trials in chronic pain are altogether difficult to design, conduct and interpret even in adult practice (Dworkin et al., 2010; Moore et al., 2013a; Polydefkis and Raja 2008). Several methodological challenges e.g. the heightened placebo response and the use of subjective outcomes are also encountered in children (Birnie et al., 2012; Dworkin et al., 2005; Dworkin

et al., 2010; Weimer et al., 2013). However, paediatric pain research may be exposed to additional challenges. First, the number of children and adolescents presenting certain types of chronic pain, e.g. neuropathic pain, is known to be very small compared to adults (Howard et al., 2014). Thus, small sample sizes and trial participants with highly variable disease profiles preclude treatment evaluation (Moore et al., 1998). Second, the choice of an adequate comparator to test therapeutic interventions is often problematic. Placebo controlled trials, the gold standard for drug testing, are not ethically acceptable in sometimes severely affected children and adolescents. In our review, placebo arms have only been implemented when testing vitamins' and antibiotics for the management of abdominal pain. On the other hand, there are currently no active comparators proven to be efficacious and considered as the standard of care in paediatric chronic pain (Walco et al., 2010; World Health Organization 2012). Third, several study features like the duration of the baseline pain intensity assessment period, washout of prohibited medications before inclusion and acceptance or not of concomitant analgesics during the trial were rarely reported in the RCTs reviewed. Yet, these are important trial features that may impact acceptance of the trial by patients/families and treating physicians and consequently influence trial recruitment. Finally, participation of patients in the RCTs was found to be rather short (median 6 months) for a condition such as chronic pain, although research needed more than 2 years to complete (median 28.5 months). Long-lasting RCTs mainly due to recruitment difficulties tend to increase research costs while losing their scientific interest.

In a significant number of RCTs included in our review the risk of bias was unclear probably because authors do not follow guidelines for reporting of RCTs and this is consistent with conclusions from previous reviews in adults (Turner et al., 2012a; Turner et al., 2012b). Our review intended to explore the potential research gap in pediatric chronic pain management and to discuss the underlying reasons for this gap. In any case, the methodological

weaknesses of the RCTs included and the heterogeneity of interventions tested prevent from drawing any conclusions on the effectiveness of the latter. Our review is also based on published RCTs and may not comprise negative studies. Therefore our results may not completely reflect research efforts to improve management of paediatric chronic pain but they shed light into the dearth and challenges of research in the field. Although there are many ways to tackle these challenges, three should be further highlighted. Properly identifying ongoing painful conditions in children and adolescents is the first step to adequate treatment. Some diagnostic tools initially developed and applied in adults should be adapted and validated in paediatrics e.g. in neuropathic pain, the DN4 questionnaire or the quantitative sensory testing (QST), whose value in clinical practice should be further explored (Howard et al., 2014; Mainka et al., 2015). Moreover, pain intensity is only one dimension of the chronic pain experience (Birnie et al., 2012). In our review, assessment of pain intensity was the primary outcome for all studies but quality of life or satisfaction with treatment was rarely assessed. Confining evaluation to merely pain intensity does not accurately reflect anticipated benefits in pain-related disability and may potentially impair testing of promising therapies (Lynch-Jordan et al., 2014; McGrath et al., 2008). Finally, international expert initiatives to define adequate methodologies and study features when performing chronic pain trials in paediatrics are greatly needed. The IMMPACT initiative (Grol et al., 2008) whose mission was to develop consensus reviews and recommendations for improving the conduct of clinical trials of treatments for pain comprised a paediatric component for outcome measures in trials. However, as opposed to adults (Dworkin et al., 2011; Dworkin et al., 2010), IMMPACT did not issue specific recommendations for the design of confirmatory chronic pain clinical trials in children and adolescents considering specific methodological challenges. Currently, only one US expert group has proposed guidance on how and when to perform RCTs in children and adolescents but merely in the context of acute pain (Berde et al., 2012). In addition,

alternative and innovative approaches to clinical trial design such as the randomised withdrawal or adaptive designs may represent more feasible and reliable options to perform clinical research in children (Baiardi et al., 2011; McQuay et al., 2008; Moore et al., 2013a). International consensus on these methods would certainly urge regulatory acceptance and contribute in developing effective treatments in children and adolescents with chronic pain.

CONCLUSIONS

This is the first review to illustrate the substantial research gap regarding analgesic interventions for children and adolescents with chronic pain. There is a lack of clinical trials to evaluate pharmacological interventions particularly in infants and in children and adolescents with long-lasting diseases. Our results underline the difficulties in conducting such trials and point out the absence of methodological guidance and implementation of innovative methodologies in this specific field.

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Author Contributions

F.K., C.A and R.B. designed the study. R.B., A.YA., E.D. and M.M. conducted data analysis. F.K., R.B. and A.YA. interpreted study results. The manuscript was initially drafted by R.B. and F.K. All authors discussed the results and commented on the manuscript.

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FIGURES LEGENDS

Figure 1. Flow chart of RCTs

Figure 2. Trends of time of the number of RCTs according to the type of evaluated intervention

Figure 3. Risk of bias assessment