

## TITLE PAGE

### **“The research gap in chronic paediatric pain:**

**A systematic review of randomised controlled trials”**

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61 **Conflicts of Interest**

62 None declared.

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## ABSTRACT

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**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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106 Appendices: 3

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110 **Significance**

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

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## TEXT

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### **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,

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

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## 178 **METHODS**

### 179 **Electronic search query**

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

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

196 secondary study outcome. Trials including both children and adults were also considered.  
197 Abstracts, letters, duplicates, preliminary publications and reviews were excluded. RCTs  
198 published in languages other than French or English were secondarily excluded.  
199 Retrieved articles were assessed by two independent authors (AY, RB), who read the titles  
200 and abstracts to identify the relevant trials. Each author independently selected the trials to be  
201 included in this review. Disagreements were resolved by discussion with a third researcher  
202 (FK). For all abstracts considered potentially relevant, full texts were retrieved. Full text  
203 article selection was independently performed by three authors (AY, RB, ED) and  
204 disagreements were resolved by consensus.

205

#### 206 **Data extraction**

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

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#### 216 **Methodological quality assessment**

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



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

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## 226 **Data analysis**

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

230

## 231 **RESULTS**

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

### 235 **General trial characteristics and study population**

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

### 244 **Clinical context**

245 Participants presented a chronic pain which was persistent in 1 RCTs (2%), recurrent in 26  
246 (45%), both in 11 (19%) but the type of chronic pain was not specified in 20 RCTs.  
247 Participants presented an underlying disease in 9 RCTs (16%). Only 29% (17/58) of RCTs  
248 specified the physio-pathological type of pain to be treated although most patients presented  
249 with more than one type of pain: nociceptive pain in 10, neuropathic pain in 8, psychogenic  
250 pain in 6 and mixed pain in 6 RCTs. Pain locations/causes are given in **Table 2** according to  
251 type of intervention. The majority of studies focused on the management of abdominal pain  
252 (64%) and headache/migraine (47%) however, 23 (40%) trials included patients with pain  
253 originating from more than one location/cause. Of note, RCTs on the management of cancer,  
254 myofascial, eye and psychosomatic pain included both children and adults.

### 255 **Trial design**

256 All RCTs aimed to evaluate the efficacy of a pain management intervention and the majority  
257 were parallel-group superiority trials (n=52; 90 %). Number of arms was 2 in 47 RCTs (81%),  
258 3 in 9 RCTs (16%) and more than 3 in 2 RCTs (3%). Median duration of study was 28.5  
259 (Q1,Q3: 21, 50) months and median individual participation was 6 months (Q1,Q3: 3, 12),  
260 respectively. **Table 3** summarizes the characteristics of the RCTs' outcome measures.  
261 Assessment of pain was the primary outcome in 86% (50/58) of RCTs (single assessment  
262 [n=12] or part of a composite outcome [n=38]), and a secondary outcome in 8% (n=8). Self-  
263 assessment of pain was privileged (95% of RCTs) and the numerical rating scale (NRS-11,  
264 50%) was the most frequently used pain scale. Other important outcomes measures such as  
265 quality of life and pain-related disability were more rarely assessed (**Table 3**).

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

269 'wash-out' period was required in 1 pharmacological RCT (7 day duration), not required in 13  
270 (20%) and not reported in 44 RCTs (78%).

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

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

#### 284 **Methodological quality assessment**

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

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

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

302

### 303 **DISCUSSION**

304 This is the first review to describe the current research on pharmacological and non-  
305 pharmacological pain management interventions in children and adolescents with chronic  
306 pain. Overall, few RCTs have been published, mainly single-institution, publicly funded trials  
307 of limited size. Only 55% were exclusively paediatric and none involved children of less than  
308 2 years of age. The majority focused on the evaluation of non-pharmacological interventions  
309 in children presenting with headache/migraine or abdominal pain. Methodological quality was  
310 poor, most probably related to the absence of adequate reporting of study features.

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

319 2 years of age. Although pain perception and its negative effects have been clearly identified  
320 in infants as young as preterm neonates (Allegaert et al., 2013), recent experimental studies  
321 advocate that neuropathic chronic pain is suppressed in the youngest and may emerge later in  
322 adolescence (Fitzgerald and McKelvey 2016; McKelvey et al., 2015). But how can we  
323 clinically confirm the absence of persistent pain in infants who are unable to verbalise pain or  
324 discomfort and without adequate tools to recognize it? Yet, the challenge of identifying and  
325 quantifying ongoing pain is not specific to the youngest as pain intensity scales used in  
326 children and adolescents have been essentially developed to evaluate acute or procedural pain  
327 (Hummel and van Dijk 2006; Palermo 2009; Stinson et al., 2006; von Baeyer and Spagrud  
328 2007). Though, it is recommended to use the same scales for chronic pain, there is no  
329 evidence on their psychometric properties in this clinical context (McGrath et al., 2008).

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

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

344 et al., 2010; Weimer et al., 2013). However, paediatric pain research may be exposed to  
345 additional challenges. First, the number of children and adolescents presenting certain types  
346 of chronic pain, e.g. neuropathic pain, is known to be very small compared to adults (Howard  
347 et al., 2014). Thus, small sample sizes and trial participants with highly variable disease  
348 profiles preclude treatment evaluation (Moore et al., 1998). Second, the choice of an adequate  
349 comparator to test therapeutic interventions is often problematic. Placebo controlled trials, the  
350 gold standard for drug testing, are not ethically acceptable in sometimes severely affected  
351 children and adolescents. In our review, placebo arms have only been implemented when  
352 testing vitamins' and antibiotics for the management of abdominal pain. On the other hand,  
353 there are currently no active comparators proven to be efficacious and considered as the  
354 standard of care in paediatric chronic pain (Walco et al., 2010; World Health Organization  
355 2012). Third, several study features like the duration of the baseline pain intensity assessment  
356 period, washout of prohibited medications before inclusion and acceptance or not of  
357 concomitant analgesics during the trial were rarely reported in the RCTs reviewed. Yet, these  
358 are important trial features that may impact acceptance of the trial by patients/families and  
359 treating physicians and consequently influence trial recruitment. Finally, participation of  
360 patients in the RCTs was found to be rather short (median 6 months) for a condition such as  
361 chronic pain, although research needed more than 2 years to complete (median 28.5 months).  
362 Long-lasting RCTs mainly due to recruitment difficulties tend to increase research costs while  
363 losing their scientific interest.

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

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

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

399

## 400 **CONCLUSIONS**

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

407

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411 Research.

412

## 413 **Author Contributions**

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

417

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580 **FIGURES LEGENDS**  
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582 **Figure 1. Flow chart of RCTs**

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

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587 **Figure 3. Risk of bias assessment**