Nonpharmacological Interventions Addressing Pain, Sleep, and Quality of Life in Children and Adolescents with Primary Headache: A Systematic Review

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Purpose: Children and adolescents with primary headache are at risk of persistent somatic symptoms and reduced quality of life (Qol) due to pain and pain-related behaviors, such as avoiding school and activities. Sleep is essential to health, and children and adolescents with primary headaches have more sleep complaints than do healthy controls. A treatment approach that addresses multifactorial causes is likely important. Nonpharmacological interventions seem promising. However, knowledge about effective strategies is limited. The objective of this review is to assess the effect of nonpharmacological interventions in randomized controlled trials (RCTs) among children and adolescents with primary headache in order to identify useful strategies.

Patients and methods: Outcome measures are pain, sleep, Qol, and coping versus no intervention or control intervention. Medline, CINAHL, EMBASE, and PsycINFO were searched for eligible trials. ClinicalTrials.gov. was searched for ongoing trials. Initial searches yielded 2588 publications. After initial screening and subsequent full-text review and quality assessment, 13 RCTs reported in 15 articles were selected for review. All reviewers independently assessed study quality using the CONSORT criteria for nonpharmacological interventions.

Results: Cognitive behavioral therapy (CBT), including education on pain-related topics, sleep, coping, and stress management, is an effective strategy for reducing headache and pain within groups over time. Fifteen studies assessed pain, 3 studies assessed sleep, 6 studies assessed Qol, and 11 studies assessed coping.

Conclusion: Strategies identified as useful were parts of CBT interventions. However, it was not possible to identify a single effective intervention addressing pain, sleep, Qol, and coping in children and adolescents with headache, primarily because sleep was infrequently addressed. Various aspects of Qol and coping strategies were assessed, rendering comparison difficult. Strategies for future interventions should include descriptions of theory-driven CBT interventions, depending on clinical setting and based on local resources, to promote a solid evidence base for nonpharmacological interventions.

Keywords: tension-type headache, migraine, pain, sleep, quality of life, coping

Introduction

Despite advances in healthcare, pain from primary headache is one of the most frequently reported health problems globally among school-aged children and adolescents.1 The pathways leading to primary headache are complex and multifactorial.2 The prevalence of headache seems to increase with age. Before the age of 12 years, minor differences exist in the frequency of headache between...
genders, but girls report headache more frequently after puberty. Tension-type headache (TTH) and migraine are considered different disorders with separate pathomechanisms that often coexist in children. The prognosis appears better for boys; in one study, 23% were migraine-free before age 25 years. Long-term studies with 20–40 years of follow-up on headache are complex to conduct due to high drop-out rates. Yet existing studies conclude that 40–70% of children who suffer from primary headache in childhood also suffer from headache in adulthood. Remission to headache-free adulthood occurs in 20–25% of children and adolescents with TTH and 15% of those with migraine.

Primary headache in children and adolescents is dominated by frequent or chronic TTH and/or migraine. They may co-occur in a single individual in varying relative importance over time, from predominant TTH to predominant migraine and vice versa. In chronic forms in which headache persists ≥15 days a month or consistently, pathophysiology is maintained by sensitization of the central nervous system in both TTH and migraine and further reinforced by lifestyle factors.

Sensitization of the nervous system is a pathomechanism from which it is very difficult to recover. Therefore, interdisciplinary educational interventions focus on health promotion and prevention to guide children and their families in paying attention to important lifestyle factors, such as sleep and coping. To reduce bias, accurate diagnosis is both possible with the International Classification of Headache Disorders (ICHD-I-III) and necessary before treatment and care. Headache as a pain condition can be treated by a team of interdisciplinary specialists, such as neuro-pediatricians, psychologists, physiotherapists, and specialist headache nurses. The team can facilitate thorough examinations, exercise planning, and education in pain mechanisms, coping strategies, and empowerment. Successful coping with stress contributes to positive headache remission, and cognitive behavioral therapy (CBT) and biofeedback seem to be effective. However, these nonpharmacological interventions are primarily available in specialists' centers, restricting broad access. Many patients worry about the side effects of preventive medications. Complementary and alternative treatment strategies are needed. It is thus important to assess the effectiveness of nonpharmacological strategies accessible to patients.

Sleep is essential for health and quality of life. Youths with primary headaches have more sleep complaints than do healthy controls. However, a paucity of research explores the mediating and moderating effects of sleep on headache in children and adolescents. Overall, the literature suggests that the association between sleep and primary headache is bidirectional and that further studies are warranted. Because children with headache suffer from sleep impairment, it is important to investigate interventions addressing or assessing sleep in this population.

Headache affects the quality of life (Qol) through impaired school, family, and emotional functioning. Headache is associated with lower academic performance. The family situation and daily routines play a major role in the child’s coping and, consequently, Qol. Reductions in Qol in children with headache were equivalent to or greater than other chronic or longer standing childhood illnesses, such as juvenile idiopathic arthritis and cancer. A child suffering from primary headache is at risk of long-term suffering in terms of lower Qol and reduced physical, social, and academic functioning.

Overall, the ability to cope influences pain, sleep, and Qol in children with headache. Lasting effects of coping in children with headache have been found after CBT, biofeedback, and relaxation therapies. Coping is concerned with efforts to manage adaptational demands and the emotions they generate. Coping has been described as a very broad concept, and no agreement exists about its conceptualization or measurement in children and adolescents. Coping is a highly relevant concept for interventions in children with headache. However, little is known about strategies, including effective and widely accessible interventions on pain, sleep, Qol, and coping in children and adolescents with primary headache. A systematic review is warranted.

Materials and Methods

The overall aims of this study are to systematically identify feasible and effective interventions for use in clinical practice and identify and evaluate the outcomes of nonpharmacological randomized interventions on 1) pain frequency, pain intensity, and pain duration; 2) sleep disturbances; 3) Qol; and 4) coping/activity limitations.

A systematic review of primary RCTs was conducted. The study was registered in the Prospero database, the international prospective register of systematic reviews (ID 104747).

Search Strategy and Study Selection

A detailed literature search of randomized trials was conducted in January 2017 and updated in August 2018. The
search included Medical Subject Headings (MeSH) and subject terms or key words (Appendix 1). The full electronic search history is available in the Supplementary Material.

Reports published in 1990–2018 studying the effects of nonpharmacological interventions in children and young people with primary headache were identified in PubMed, CINAHL, PsycINFO, Cochrane, and SveMed Plus databases and supplemented by a snowball search technique. Reference lists were scrutinized, and unpublished literature was identified and reviewed by contacting authors of abstracts reported in conference proceedings and ClinicalTrials.gov searches. Reference lists of prior systematic reviews and other relevant papers were manually examined. The search was restricted to English language.

The following selection criteria were used for selection of the studies:

- Peer-reviewed original articles
- RCT published in full text

Participants

- Study populations comprised children and adolescents aged 7–18 years
- Participants were diagnosed with primary headache, tension-type headache (TTH) or migraine

Interventions

- Nonpharmacological interventions as standalone approaches or in combination with other treatments

Outcome measures

- Primary outcomes were headache and pain reduction; secondary outcomes were sleep, Qol, and coping.

Synthesis of Evidence

Studies of mental illness, disability, and acute conditions, anxiety disorder, attention deficit hyperactivity disorder and other psychiatric diagnoses, pharmacology, melatonin and solely or primarily biofeedback were excluded, as were school-based studies (Appendix 2, PICO criteria).

The study selection process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. Search results were managed using COVIDENCE software, and duplicates were removed. Full text of relevant studies was retrieved and studies considered eligible for review were determined. Multiple reports from the same study were linked. A data extraction sheet was used in concordance with inclusion and exclusion criteria.

Quality Appraisal and Data Extraction

Validity, design characteristics, and research quality of included trials were evaluated by all authors according to the CONSORT checklist for nonpharmacological interventions,\(^\text{40,41}\) the extension suggested by Hoffmann\(^\text{42}\) and the International Classification of Headache Disorders (ICHD).\(^\text{1,2}\) For articles selected for full review, data were extracted on authors, title, purpose, study population, and sample size and outcome measures of pain, sleep, Qol, and coping. Interventions, results, and child/parent and health professionals’ satisfaction with an intervention were retrieved (Table 1). Finally, data on cost analysis, recruitment and retention, and other relevant information for health-care professionals were also retrieved.

Results

A total of 2588 publications were identified. After removing duplicates and title and abstract screening, 247 full-text articles were assessed for eligibility. Thirteen RCTs reported in 15 articles were included (Figure 1).

Eight studies were conducted in the USA, two in Canada, and five in Germany (Table 1). Trials enrolled 26–135 participants aged 7–18 years. Eligibility was confirmed by ICHD-criteria I–II in seven studies and by neurologist assessment, parents, or unspecified in four studies.

Nine studies met the CONSORT criteria.\(^\text{40}\) No studies blinded researchers; one study blinded participants.\(^\text{43}\) Seven studies had low risk of bias related to randomization procedures.\(^\text{43–49}\) Findings were organized into the four outcomes of interest: pain, sleep, Qol, and coping. Figure 2 depicts assessment instruments used in included studies. Assessments were conducted 2–4 weeks before baseline and up to 12 months post intervention.
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<tr>
<td>McGrath 1992 Canada&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RCT with 3 arms To evaluate a controlled home-based self-administered program on pain Migraine for 3M N=87, 11–18 years T1:24 T2:23 Control: 26</td>
<td>4-week baseline, post-treatment and at 1, 3, and 12 M follow-up</td>
<td>Headache frequency, headache intensity (6-point scale) by headache diary</td>
<td>Minutes of therapist contact Depression scores (instrument not identified)</td>
<td>T1: 8-week self-administered program with coping manual and tape for relaxation. Weekly telephone contact. T2: T1 plus individual clinic meetings Control: List of triggers, weekly telephone contact</td>
<td>T1: 50% improvement T2: 47.8% improvement Control: 5.8% improvement Stress management treatment is effective in reducing headache at 1-year follow-up. Self-management is more efficient</td>
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<tr>
<td>Barry 1997 Canada&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RCT To evaluate effect of a group based multi-dimensional treatment program on pain and coping Episodic headache ≥2/month N=29, 7–12 years and parents T:12 Control:17</td>
<td>3-week baseline, post-treatment, 3M telephone follow-up</td>
<td>Headache frequency, intensity and duration by headache diary</td>
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<td>T: Two sessions of 90 min over 3 weeks in groups of 5–8 children. Play, relaxation, visualization, and cognitive behavioural strategies. Control: Waiting list</td>
<td>T: 4/36 reduced headache by 50%</td>
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<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample Size</td>
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<tr>
<td>Kröner-Herwig 2002</td>
<td>RCT with 3 arms</td>
<td>Germany</td>
<td>75</td>
<td>10–14 years</td>
<td>To compare therapist-administered group training with home-based manualised self-help training on pain and coping</td>
<td>Episodic headache ≥2/ M by ICHD-I N=75, 10–14 years T1: 29 T2: 27 Control: 19</td>
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<tr>
<td>Cottrell 2007</td>
<td>RCT with 2 arms</td>
<td>USA</td>
<td>34</td>
<td>12–17 years</td>
<td>To examine the feasibility of telephone administered behavioural migraine management vs drug therapy</td>
<td>Migraine 2–6/ M by ICHD-II N=34, 12–17 years T1: 18 T2: 16</td>
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<th>First Author Year Location</th>
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<tr>
<td>Palermo 2009 USA&lt;sup&gt;48&lt;/sup&gt;</td>
<td>RCT with 2 arms</td>
<td>To evaluate an Internet-delivered family CBT vs wait list on pain, activity and well-being</td>
<td>Chronic idiopathic pain over the previous 3 M N=48, 11–17 years</td>
<td>T: 26 (12 with headache) Control: 22</td>
<td>7 days pre-treatment: post-treatment and at 3 M follow-up</td>
<td>Pain frequency, pain intensity (NRS 0-10) by pain diary</td>
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<td>Study</td>
<td>Design/Population</td>
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<td>Outcome Measures</td>
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<td>Gerber 2010</td>
<td>RCT with 2 arms</td>
<td>Episodic headache &lt;15 days/M by ICHD-II</td>
<td>Headache frequency, intensity and duration by headache diary, headache questionnaire (PRRS)</td>
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<td></td>
<td>Germany/USA</td>
<td>N=34, 7–16 years and parents</td>
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<td>KINDL</td>
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<td>T1: 19 T2: 15</td>
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<td>Daily living activity diary</td>
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<td>4-weeks baseline and 6 and 12 M follow-up</td>
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<td>by headache diary, headache questionnaire (PRRS)</td>
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Significant long-term reduction in headache frequency and intensity for both groups. No significant differences between groups though biofeedback gave most reduction in H frequency. Both groups revealed improved QoL over time. Group training is recommended as is involvement of parents.

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<tr>
<th>First Author and Year</th>
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<tr>
<td>Siniatchkin 2011</td>
<td>RCT with 2 arms</td>
<td>Migraine without aura by ICHD-II</td>
<td>26, mean age 12 years and parents</td>
<td>8-week baseline and after 8 weeks of intervention</td>
<td>T1: MIPAS-Family: Eight sessions of 90 mins for children. 4 sessions of 120 mins for parents: Stress coping and sensory coping exercises. T2: Biofeedback frontal EMG and thermal Biofeedback with animations. 20 sessions of 50 mins</td>
<td>No significant between-group differences. Biofeedback most reduced H frequency. Both groups had improved QoL over time. Group training and involvement of parents recommended. Significantly reduced migraine frequency and intensity for both groups without between-group difference. Normalized iCNV habituation for MIPAS-Family training. MIPAS-Family leads to reduced symptoms and improved coping and QoL.</td>
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<td>(Additional assessment and analysis of Gerber 2010)</td>
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**Note:**
- **Timeline:** Pain (frequency, intensity and duration by headache diary), Sleep quality registration questionnaire, KINDL, Daily living activity diary.
- **Intervention:** T1: MIPAS-Family: Eight sessions of 90 mins for children. 4 sessions of 120 mins for parents: Stress coping and sensory coping exercises. T2: Biofeedback frontal EMG and thermal Biofeedback with animations. 20 sessions of 50 mins.
- **Results Conclusion:** No significant between-group differences. Biofeedback most reduced H frequency. Both groups had improved QoL over time. Group training and involvement of parents recommended. Significantly reduced migraine frequency and intensity for both groups without between-group difference. Normalized iCNV habituation for MIPAS-Family training. MIPAS-Family leads to reduced symptoms and improved coping and QoL.
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<td>Trautmann 2010</td>
<td>RCT with 3 arms</td>
<td>Primary headache ≥2/M</td>
<td>4 weeks pre- and post-treatment and at 6 M follow-up</td>
<td>KINDL-R, Strength and Difficulties Questionnaire (SDQ), Pain Catastrophizing Scale, Medication</td>
<td>Examine efficacy of a controlled internet-based self-help training on pain, pain-catastrophizing and well-being. Control: 19</td>
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<td>N=65, 10–18 years. T1: 24</td>
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<td>4 weeks and duration by headache diary.</td>
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<td>T2: 22</td>
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<td>Headache frequency, intensity and duration by headache diary.</td>
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<td>Koenig 2013</td>
<td>RCT with 2 arms</td>
<td>Frequent or chronic TTH and migraine by ICHD-II</td>
<td>8-weeks baseline, 8 weeks post-treatment and at 8 weeks and 6 M follow-up</td>
<td>KIDS-SCREEN-27, SDQ, Hertinghausen Satisfaction Questionnaire</td>
<td>Investigate the effect of music therapy on pain, strengths and difficulties and satisfaction.</td>
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<td>N=78, 12–17 years and parents T: 40</td>
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<td>Subjective experience of coping with headache improved more in T1 and T2.</td>
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<td>Control: 38</td>
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<td>Significant reduction in headache frequency and duration for all groups was sustained at 6 M. Significant improvement in pain catastrophizing.</td>
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<td>Significant reduction in headache frequency and duration for all groups was sustained at 6 M. Significant improvement in pain catastrophizing. No significant between-group differences. No significant change on psychological parameters. Significant treatment satisfaction over time.</td>
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<td>First Author Year Location</td>
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<tr>
<td>Powers 2013 USA $^1$</td>
<td>RCT with 2 arms</td>
<td>Chronic migraine by ICHD-II PedMIDAS ≥ 20 points N=135, 10–17 years T1: 64 T2: 71</td>
<td>28-day baseline and after 20 weeks and at 3, 6, 9 and 12 M follow-up</td>
<td>Headache frequency, intensity (VAS Scale) and duration and associated symptoms by headache diary Sleep is part of Headache Education</td>
<td>Treatment credibility questionnaire Psychiatric interview; child and parent questionnaires T1: CBT 8 sessions over 8 weeks and 2 booster sessions 1mg/kg/day of amitriptyline T2: Headache Education (HE) 10 sessions 1mg/kg/day of amitriptyline</td>
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<tr>
<td>Kroner 2016 (secondary analysis of Powers 2013) $^2$</td>
<td>To determine if participants in a previous trial needed less preventive medication</td>
<td>Chronic migraine by ICHD-II PedMIDAS ≥ 20 N=135, 10–17 years T1: 64 T2: 71</td>
<td>28-day baseline. Follow-up after 20 weeks and at 3, 6, 9, and 12 M</td>
<td>Headache frequency, intensity (VAS Scale) and duration by headache diary</td>
<td>Benchmark for no longer needing medication: headache ≤1 day/week</td>
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<tr>
<td>Rapoff 2014 USA</td>
<td>RCT with 2 arms</td>
<td>To evaluate a CD-ROM with cognitive-behavioral self-management strategies vs an educational CD-ROM on pain, disability and QoL</td>
<td>Migraine ≥ 1/week by ICHD I+II; child behavior checklist N=35, 7–12 years T1: 18 T2: 17</td>
<td>Two-weeks baseline, post-intervention and at 3 M follow-up</td>
<td>Headache frequency, intensity (VAS Scale) and duration by headache diary</td>
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<tr>
<td>Hickman 2015 USA</td>
<td>RCT with 2 arms</td>
<td>To pilot the effects of a brief cognitive behavioral skills-building intervention on feasibility, disability and well-being</td>
<td>Chronic daily headaches and mild-to-moderate depressive symptoms by unspecified headache classification. Beck Youth Depression Inventory, N=36, 13–17 years and parents T: 18 Control: 18</td>
<td>Pre- and post-treatment measures</td>
<td>Parent Perception of Pain Interference (PPPI)</td>
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<th>First Author Year Location</th>
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RCT with 2 arms
To evaluate the effect of an Internet-delivered CBT intervention compared with Internet education in a large multicenter cohort on 1) daily activity limitations and 2) pain, emotional functioning, sleep quality, and parental behavior.

Chronic idiopathic pain for 3 M N=273 (19 with headache), 11–17 years and parents T1: 138 T2: 135

Pre- and post-intervention and at 6 and 12 M

Pain frequency and pain intensity (NRS=10) by pain diary Parents responses to pain behaviours ARCS

Sleep quality by Adolescent Sleep Wake Scale (ASWS)

Emotional functioning by Parents responses to pain behaviours (BAPQ)

CALI Miscarried helping by Helping for Health Inventory (HHI-Pain)

Treatment Satisfaction by Treatment Evaluation Inventory, short form

T1: 9 hrs of Internet-delivered family based CBT including web-based Management of Adolescent Pain (WEB-MAP) with 5 functional components T2: 9 hrs of Internet-delivered pain education by WEB-MAP with 2 functional components.

From baseline to 6 M follow-up, T1 had significantly greater reductions in activity limitations. T1 had a minor pre-post treatment effect on emotional functioning, but it was not sustained. T1 had significantly greater improvement in sleep quality from baseline to 6 M follow-up. T1 had a significantly greater reduction in parental protective behavior.

Abbreviations:
ARCS, Protect subscale from Adult Response to Children’s Symptoms; ASWS, Adolescent Sleep Wake Scale; BAPQ, Bath Adolescent Pain Questionnaire; BAP-PIQ, Bath Adolescent Pain-Parent Impact Questionnaire; BYI-II, Beck Youth Inventories; CALL, Child Activity Limitations Interview; CBT, cognitive behavioural therapy; CDI, Childhood Depression Inventory; HE, headache education; ICHD, International Classification of Headache Disorders; M, month(s); MSQL_A, Migraine-Specific Quality of Life - Adolescent; PED-MIDAS, Pediatric Migraine Disability Assessment; QOL, quality of life; RCADS, Revised Childhood Anxiety and Depression Scale; RCMAS-2, RCT, randomised controlled trial; SDQ, Strengths and Difficulties Questionnaire; T, treatment; TTH, tension-type headache; WEB-MAP, web-based Management of Adolescent Pain.
Strategies
Most treatment interventions were based on CBT and most control interventions were education. Table 2 identifies techniques contributing to effectiveness across interventions, inspired by Abraham and Michie’s taxonomy of behavior change techniques. Strategies to reduce pain were included in CBT, and educational interventions sought to influence children’s and parents’ perceptions of pain, as indicated by the assessments of outcomes on pain catastrophizing, pain perception, and parents’ response to pain behavior (Figure 2). Two studies described strategies aimed at improving sleep by education. Strategies directed at the ability to cope included education on coping with stress, images of self-concept, demonstration of relaxation skills, skills to reduce and manage stress and problem solving or were included in CBT. Figure 3 depicts effective components of CBT.

Pain Outcomes and Assessment Tools
Trautmann and Kröner-Herwig used data from a pain-catastrophizing scale, and the intervention was associated with significant reduction in pain catastrophizing. Koenig et al collected information from a pain perception questionnaire but found no significant change in psychological parameters. Hickmann et al found that parents’ perception of pain interference (PPPI) was unchanged. Law et al gathered information about parents’ responses to pain behavior and protectiveness (ARCS) and found statistically significant pre-post improvements in parent protective behaviors. Palermo et al also used the ARCS, as well as parents’ pain-related impact (BAPO-PIQ), and found a small-to-medium significant pre-post reduction in parent protective behavior (d=0.49). The authors also examined miscarried helping with the Helping for Health Inventory and found a small pre-post effect from CBT (d=−0.30).

Figure 1 Flow chart of the search and selection process.
Pain was assessed in 12 of 13 studies by daily self-reported headache or pain diaries to monitor headache frequency, intensity, and duration.\textsuperscript{43,45–49,51–58} Headache frequency was most frequently used as the primary self-reported outcome, as recommended by Andrasik et al and Penzien et al.\textsuperscript{59,60} McGrath et al\textsuperscript{56} used a 6-point Likert scale to assess headache intensity. Five studies measured intensity by a 0–10 visual analogue scale.\textsuperscript{43,49,51,54,55} Palermo et al used a 0–10 numeric rating scale to assess headache intensity.\textsuperscript{47,48}

Ten studies reported statistically significant long-term within-group reductions in headache frequency and intensity or duration from interventions comprising CBT\textsuperscript{44,46,48,49,51–55,57,58} and, in one study, music therapy.\textsuperscript{43} None reported a statistically significant between-group difference.

Eight studies calculated effect sizes for primary outcomes, reported as Cohen’s \(d\), mean effect size (ES) or ANCOVA (\(n\)):
- Headache pre-post CBT, \(ES = 0.5; d = 1.0\);\textsuperscript{52} pre-post Internet treatment for migraines, \(d = 1.0\);\textsuperscript{53} pre-post Internet treatment for activity limitations, \(n^2 = 0.17; d = 0.88\);\textsuperscript{56} child report of headache frequency after a multi-modal behavioral training program (MIDAS), \(d = 0.88\);\textsuperscript{54} headache frequency with CBT, \(ES = 0.24; d = 0.88\);\textsuperscript{49} headache severity post-Headstrong intervention, \(ES = 0.7; d = 0.88\);\textsuperscript{55} headache frequency pre-post Internet-delivered CBT, \(d = 0.40; d = 0.88\);\textsuperscript{46} and pre-post Internet-delivered CBT for activity limitations, \(d = -0.25; d = -0.25\).\textsuperscript{47}

A single study\textsuperscript{46} calculated the number needed to treat (NNT) for \(\geq 50\%\) headache reduction; for the comparisons of CBT and education and of applied relaxation and education, respectively, it was 2.0 (95\% confidence interval [CI], 1.3–4.7) and 5.2 (95\% CI: 2.2–\(\infty\)), calculated by the Cook and Sackett method.\textsuperscript{61} Four studies reported results from intention-to-treat analyses (ITT).\textsuperscript{43,46,49,51} Five studies reported a preliminary power calculation.\textsuperscript{46–48,51,55}

Medication
Cottrell et al\textsuperscript{53} used migraine medication as an active control group and found an effect size of \(d = 1.2\) for migraines per month. Powers et al\textsuperscript{51} and Kroner et al\textsuperscript{45} used CBT plus amitriptyline as the primary intervention. Kroner et al\textsuperscript{45} collected data using a benchmark of headache \(\leq 1\) day/week indicating that preventive medication was no longer needed. In the CBT and headache education groups, respectively, 72\% and 52\% of participants reached the benchmark at 12 months of follow-up.

Sleep Outcomes and Assessment Tools
Two of the included studies examined the association between primary headache and sleep. Outcome measures were the Adolescent Sleep Wake Scale (ASWS) which assesses adolescents’ perception of sleep quality\textsuperscript{47} and actigraphy.\textsuperscript{46} A third study assessed sleep habits as part of the headache education received by the control group.\textsuperscript{51} Ten studies did not assess or evaluate sleep.
Quality of Life Outcomes and Assessment Tools
QoL was assessed in 10 studies by stress instruments, emotional functioning, a migraine-specific instrument, KINDL, KINDL-R, KidsScreen, PedMidas, or PedsQl. QoL was described in terms of decreasing stress symptoms by Kröner-Herwig and Denecke and Hickman et al and increased emotional functioning by Palermo et al.

Table 2 Characteristics of Intervention Delivery Modes, Techniques, and Control Interventions

<table>
<thead>
<tr>
<th>Authors</th>
<th>Relaxation</th>
<th>CBT</th>
<th>Education</th>
<th>Other</th>
<th>Waiting List Control</th>
<th>Telephone Contact</th>
<th>Web Based (CD Rom)</th>
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<th>Individual Self Management</th>
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Notes: *Plus amitriptyline in both groups. ²Specialised headache treatment in both groups.
Abbreviations: C, control intervention; X, intervention technique; d, delivery mode.

Figure 3 Components of effective cognitive behavioral theory.
Coping Outcomes and Assessment Tools
Interventions demonstrating an effect on coping were found in 10 studies. Coping was assessed in six studies by validated instruments. Three studies used PedMIDAS to assess disability and school absence. Three studies assessed the activity of daily living with CALI, a pain-specific instrument. Three studies did not address coping. In five studies, assessments of coping (and functional status, comorbidities, anxiety, and depression) were undertaken with various instruments.

Discussion
Thirteen RCTs included in this review, reported in 15 articles, examined the effect of nonpharmacological treatment of primary headache (migraine or TTH) on pain as a primary outcome and changes in sleep, QoL, and coping as secondary outcomes in children and adolescents aged 7–18 years. The studies used different approaches to perform CBT and various control groups.

Ten of 13 studies showed a significant within-group reduction in pain (headache frequency and intensity or duration) over time but no between-group differences that would indicate a general treatment effect. None of the included studies examined all outcomes of interest, i.e., pain, sleep disturbance, changes in QoL, and coping. Therefore, no specific strategy can be identified as superior; the choice of strategy will depend on the clinical setting and patient characteristics.

Sleep was infrequently evaluated. Two of 13 studies incorporated sleep education into CBT. One found a small but significant effect on sleep quality at follow-up; the other did not. In addition to pain reduction, better functional outcomes in daily life are vital for children and adolescents with primary headache. In the included studies, different aspects of QoL and coping strategies were measured; in some studies, the concepts of QoL and coping overlapped, rendering comparison difficult. Clearly defined outcome measures of QoL and coping are required to compare CBT intervention studies. Despite these limitations, nonpharmacological interventions seem to be well accepted, and feasible and effective components and strategies can be identified.

Participants
Baseline characteristics of participants reflected variation in age (7 to 18 years), headache type, and comorbidities (e.g., anxiety and depression), as well as illness severity. Three studies stratified participants to tailor age- and gender-relevant interventions. These and other stratifications seem appropriate in this population to generate and implement evidence-based treatments in clinical practice. As stratification will reduce the statistical power in studies with small sample sizes, multi-site studies may be a solution. In addition, the total number of participants in the included studies, which were published in 1992–2016, was 723, and dropout rates were substantial. Thus, larger multicentre studies are needed to generate valid conclusions.

Although nine of the included studies adhered to the CONSORT criteria, none fully adhered to the guidelines. A recent systematic review by Boukhlied et al on RCTs on chronic pain in children supports this finding. This is consistent with previous findings from studies with adults. Blinding of participants to a nonpharmacological intervention is challenging. However, blinding of outcome evaluators is possible. Following CONSORT recommendations, as well as other recommendations for pediatric headache research, can improve research validity and reliability. In addition, recommendations from The Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) stress that core outcome domains should be considered when designing pain clinical trials for acute and recurrent/chronic pain.

Strategies and Successful Operational Components of Feasible and Effective Interventions
The results in this review indicate that CBT can reduce headache and pain symptoms significantly within groups and reduce parental protective behavior to some degree. However, when considering between-group differences and the scale of symptom reductions, the effects of treatments are less clear. No interventions described in depth the theoretical framework, even though CBT and music therapy are theory-based interventions. However, most studies described the intervention techniques.

Primary headaches are due to multifactorial somatic and psychosocial causes in different headache groups and can change over time. The effects of interventions can also dampen over time. The ideal intervention should encompass all causal elements of primary headache. This review highlights the fact that biopsychosocial interventions targeting children and adolescents with primary headache are complex.
The paradoxical finding of no between-group differences for any interventions in the included reports but significant within-group differences could be because both treatment and control interventions included useful strategies and modalities. To identify effective interventions, future studies should adhere to an identified theoretical framework and compare the intervention with another established treatment. Mindfulness-based stress reduction may be effective in the treatment of headache but was not tested in any of the included studies.67

Outcomes

Pain

Penzien et al46 stress the importance of \( \geq 50\% \) improvement to exceed a possible placebo effect that might reach levels of \( \geq 30\% \).68 In the review reported here, a consensus existed on using 50% as a standard. However, the placebo effect may play a larger role in future research, since what works for patients is most important. None of the studies report between-group differences. Appropriate statistical power is essential to reporting statistically significant findings and effect sizes.69 A preliminary power calculation was reported by only 5 of 13 included studies.46–48,51,55 Statistical power and a consensus on how to compute effect sizes in neuropsychological studies are important. One study49 calculated NNT for the 50% standard, which could also be a good way to calculate effects.69

Sleep

The American Academy of Sleep Medicine recommends amounts of sleep per 24 hrs that children and adolescents should have on a regular basis to promote optimal health outcomes.19 Children aged 1–2 years should sleep 11–14 hrs, children aged 3–5 years should sleep 10–13 hrs, children aged 6–12 years should sleep 9–12 hrs, and adolescents aged 13–18 years should sleep 8–10 hrs.19 None of the included studies reported the amount of sleep study participants obtained, except for Law et al,46 who reported that participants aged 11–18 years of age in both treatment groups had insufficient sleep, averaging about 6 hrs per night. To investigate the impact of sleep on primary headache, a sleep evaluation must be performed before any intervention.

In this review, sleep was only addressed in 3 of 13 studies, evaluated by questionnaire in one study,47 and by actigraphy in another.46 Two of three recent studies included a sleep intervention as part of the CBT program. One study among a mixed chronic pain group in which just 7% of participants had headache alone found slightly better sleep quality in the CBT group, compared to participants receiving an educational strategy.47 In another study evaluating sleep by actigraphy among patients with primary headache, no between-group changes in sleep quality were found.46 In fact, participants spent a substantial amount of time awake in bed at night, as assessed by pre-treatment actigraphy. Screen time was not evaluated in these studies. None of the studies reported associations between primary headache and sleep.

Primary headaches (migraine and TTH) have been associated with sleep disturbance in observational studies. The association is bidirectional, with primary headaches influencing sleep and disturbed sleep influencing primary headaches.70,71 Sleep disturbances have been reported in as many as 65–73% of pediatric patients with chronic headache.23,72

A recent retrospective clinical study assessing the prevalence and occurrence of possible migraine trigger factors in children and adolescents with migraine showed that stress was the most frequently reported trigger factor (75.5%), followed by lack of sleep (69.6%).73 The same influence of headache triggers (poor sleep and emotional distress) was shown in a non-clinical population of children and adolescents by Bruni et al.74 Few studies have investigated the relationship between sleep and headache using a longitudinal design. Elements of primary headache may cause or aggravate a disturbed sleep schedule, and disturbed sleep may interfere with resolution of or trigger a primary headache. Bruni et al75 randomly assigned migraineurs aged 5–14 years to two groups: one received sleep hygiene recommendations and the other did not. After 6 months of follow-up, the sleep hygiene group reported lower mean headache duration than did the control group, suggesting that better sleep quality led to altered migraine patterns. Although this study did not directly measure the effects of sleep disturbance on migraines, it supports the direction of the relationship (i.e., sleep disturbance can negatively influence migraine).

Heyer et al76 performed a longitudinal prospective study of 52 children aged 10–18 years with episodic migraine; some participants also had TTH. The authors compared the frequency and headache characteristics of headache days with sleep disturbance to headache days without sleep disturbance. Outcomes were measured with an Internet-based, 90-day headache diary, self-rated headache intensity and Ped-MIDAS score, and
reports of sleep disturbances directly related to proximate headaches. Twenty-one percent of participants reported headaches, and 13.9% reported sleep disruptions directly related to a proximate headache. The higher the Ped-MIDAS scores, the more days with sleep disturbances related to headache. The maximum proportion of headache days that impacted sleep was 32%. Headache intensity (P = 0.009) and timing of headache onset (P < 0.001) predicted sleep disturbances.

Many studies investigating the relationship between primary headaches and sleep disturbances have applied either Internet-based headache diaries or questionnaires assessing sleep difficulties or trigger factors. Few have applied objective measurements such as actigraphy for monitoring sleep patterns. This is an important area for future study. Regular insufficient sleep is associated with attention, behaviour and learning problems, which may aggravate primary headache and influence Qol and coping strategies.

**Qol**

Health-related Qol is a multidimensional concept that reflects the impact of disease and treatment on the patient’s subjective evaluation of functioning and well-being. Studies included in this review used a variety of approaches to capture the impact of an intervention on family functioning and daily life for children and adolescents suffering from headache. Most reported significant headache reduction regardless of group allocation, suggesting that increased attention on the child suffering from headache can positively impact the child and family.

Parents were included in five studies. The underlying assumption was that the efficacy of the therapeutic intervention would increase by integrating parents into treatment programs. Incorporating family daily activities into treatment programs would facilitate parents becoming trainers, helping children to use learned techniques at home between program sessions. No reported result supported this assumption. However, Sinitchkin et al found improved transfer of learned strategies into daily life in the MIPAS-Family group, improving the child’s ability to cope with stressful situations, adjust to aversive stimuli, and even prevent migraine attacks. Gerber et al found that parents were increasingly motivated to participate in training as training proceeded, but they also lacked relevant knowledge about the child’s headache. This lack of knowledge may lead to underestimating the child’s complaint or parental behavior that exacerbates the chronicity of the child’s condition, emphasizing the value of including parents in the treatment of children or adolescents.

Organization of the interventions may also determine effectiveness. Kröner-Herwig and Denecke argue that therapist-conducted training is preferable to a self-help format because it is more efficient and appealing to children. However, they also report dropouts due to scheduling difficulties, indicating that the logistics of bringing children to appointments at the hospital is a barrier that may lead to noncompliance. Similarly, Palermo et al found that parents were better integrated in a web-based treatment program because interventions in a clinical setting were time-consuming and harder to integrate into daily family routines.

In terms of the feasibility of training migraine management skills in a group setting for adolescents, Cottrell et al demonstrated that a telephone-administered behavior treatment was associated with clinically significant improvements in migraine that did not reach statistical significance due to small study size and the lack of a control group. The potential value of low-intensity treatment modalities provided by telephone or web may be enhanced by their low cost and adaptability to the daily lives of adolescents and families.

**Coping**

Coping can be characterized as engagement or disengagement coping. The authors define engagement coping as “aimed at dealing with the stressors or the resulting distress emotions” and disengagement coping as “aimed at escaping from dealing with the stressors or the resulting distress emotions”. In this review, all effective interventions included components of engagement coping strategies, such as cognitive restructuring and stress coping, emotional and self-reassurance techniques, or problem-solving or communicative strategies. This finding indicates that numerous components of effective interventions promote coping. Therefore, the accessibility of local resources could guide the choice of engagement coping strategies in future interventions to treat headache in children.

Headache in childhood can be viewed as a biopsychosocial condition because sleep and other stressors can contribute to it. A biopsychosocial perspective adheres to the idea that pain is a result of interactions between nociceptive, sociocultural, behavioral, and cognitive factors. All these domains should be incorporated when identifying relevant outcomes, rather than relying on pain as the primary outcome. Studies included in this review showed substantial variation in outcomes. In two studies, activity limitations, as assessed by CALI, were...
the primary outcome, rather than the impact of pain from headache. Validation of CALI found that children with headache had more limitations on routine activities, such as going to school, reading, schoolwork, watching TV, and eating regular meals, than did children with abdominal pain, back pain, musculoskeletal pain, or other pain diagnoses. This finding makes CALI useful for targeting interventions and measuring outcomes in future interventions in children with headache.

**Parental Involvement**

Five studies gathered additional information about phenomena associated with pain, such as pain catastrophizing, pain perception and interference, and parental pain behavior. Three studies included proxy assessments by parents: PPPI, parents’ response to pain behavior (ARCS protect subscale) or parents’ response to pain. 44,46,47 Children and, to a lesser extent, adolescents generally depend on their parents for daily assessments of symptoms and treatment. Parents’ personal pain histories could confound a child’s pain outcome; cross-sectional studies find that headache in childhood can be associated with parents’ pain history. 52 This argues for the inclusion of parents in future interventions.

**Satisfaction and Feasibility**

Patient perspectives on experience of and satisfaction with interventions were sought in several studies, 43,46,48,49,51,53 indicating the importance of patient acceptability. Nonadherence to pediatric interventions has a negative impact on implementation of evidence-based interventions because studies with small sample sizes lack power. A recent review of theoretical frameworks in pediatric adherence-promoting interventions found that there is a need for theory-driven studies in pediatrics. 83

**Other**

Three studies were web-based interventions 46–48 and applied gamification techniques. 84 Web-based interventions have the potential to reach many more children and adolescents, overcoming problems related to attrition. However, they may quickly become outdated. In addition, increased screen time may influence headache mediated by less sleep. In a cross-sectional study of 1004 Italian students aged 10–16 years, Cerutti et al found that “results highlighted the potential impact of excessive Internet and mobile use, which ranges from different types of headache to other somatic symptoms”. 85 Further studies are needed to confirm these findings and to assess the need for promoting preventive health interventions, especially in school settings. Sleep was not assessed in this study. Screen time was not assessed in any study.

Primary headache is multifactorial. It not possible to identify a single feasible and effective intervention addressing pain, sleep, QoL, and coping in children and adolescents with headache, primarily because sleep is insufficiently addressed. We identified risk of bias in more than a third of the studies due to lack of specified randomization procedures, blinding, ITT analyses, power calculations and effect sizes, or adequate description. Varying aspects of QoL and different coping strategies were assessed, making an overall comparison difficult. However, effective components and strategies were identified. CBT, including education on pain-related topics, sleep, coping, and stress management, is effective at reducing headache and pain within groups over time.

Future interventions should elaborate on detailed descriptions of theory-driven cognitive-based therapies to promote a solid evidence base for nonpharmacological interventions. Sleep examination and perspective of patients and families were identified as important components in future evaluations of primary headache interventions.

This review was conducted according to PRISMA guidelines and the protocol was published. Three independent reviewers validated the inclusion and exclusion process. Limitations include the exclusion criteria and restriction to English-language-only studies.

**Conclusion**

Useful strategies that improve pain, sleep, QoL, and coping in children and adolescents with primary headache have been identified. None of the studies incorporated examination of all aspects of pain, sleep disturbance, changes in QoL, and coping. Therefore, no specific strategy can be identified as superior; the choice of intervention will depend on clinical setting and patient characteristics. In clinical practice, interventions should be based on local resources. Developing and testing new types of interventions should include the perspectives of patients and their families. Future research should adhere to rigorous methods and meaningful standardized patient outcomes.

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References


