

## Symptomatic Treatment of Migraine in Children: A Systematic Review of Medication Trials

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**ABSTRACT.** *Objective.* Treatment of pediatric migraine includes an individually tailored regimen of both nonpharmacologic and pharmacologic measures. The mainstay of symptomatic treatment in children with migraine is intermittent oral or suppository analgesics, but there is no coherent body of evidence on symptomatic treatment of childhood migraine available. The objective of this review is to describe and assess the evidence from randomized and clinical controlled trials concerning the efficacy and tolerability of symptomatic treatment of migraine in children.

*Design.* Systematic review according to the standards of the Cochrane Collaboration.

*Methods.* Databases were searched from inception to June 2004. Additional reference checking was performed. Two authors independently selected randomized and controlled trials evaluating the effects of symptomatic treatment in children (<18 years old) with migraine, using headache (HA) clinical improvement as an outcome measure. Two authors assessed trial quality independently by using the Delphi list, and data were extracted from the original reports by using standardized forms. Quantitative and qualitative analysis was conducted according to type of intervention.

*Results.* A total of 10 trials were included in this review, of which 6 studies were considered to be of high quality. The number of included participants in each trial ranged from 14 to 653, with a total of 1575 patients included in this review. Mean dropout rate was 19.8% (range: 0–39.1%), and the mean age of participants was  $11.7 \pm 2.2$  years (range: 4–18 years).

All studies used HA diaries to assess outcomes. In most studies, a measure of clinical improvement was calculated by using these diaries. Improvement often was regarded as being clinically relevant when the patients' HA declined by  $\geq 50\%$ .

Regarding oral analgesic treatment, the effectiveness of acetaminophen, ibuprofen, and nimesulide were evaluated. When compared with placebo, acetaminophen (relative risk [RR]: 1.5; 95% confidence interval [CI]: 1.0–2.1) and ibuprofen (pooled RR: 1.5; 95% CI: 1.2–1.9) significantly reduced HAs. We conclude that there is moderate evidence that both acetaminophen and ibuprofen are more effective in reduction of symptoms 1 and 2

hours after intake than placebo with minor adverse effects. No clear differences in effect were found between acetaminophen and ibuprofen or nimesulide.

Regarding the nonanalgesic interventions, nasal-spray sumatriptan, oral sumatriptan, oral rizatriptan, oral dihydroergotamine, intravenous prochlorperazine, and ketorolac were evaluated. When compared with placebo, nasal-spray sumatriptan (pooled RR: 1.4; 95% CI: 1.2–1.7) seemed to significantly reduce HAs. We conclude that there is moderate evidence that nasal-spray sumatriptan is more effective in reduction of symptoms than placebo but with significantly more adverse events. No differences in effect were found between oral triptans and placebo. All medications were well tolerated, but significantly more adverse events were reported for nasal-spray sumatriptan compared with placebo.

We also conclude that there is moderate evidence that intravenous prochlorperazine is more effective than intravenous ketorolac in the reduction of symptoms 1 hour after intake. No differences in effect were found between oral dihydroergotamine and placebo.

*Conclusions.* Acetaminophen, ibuprofen, and nasal-spray sumatriptan are all effective symptomatic pharmacologic treatments for episodes of migraine in children. The new frontier for symptomatic treatment is likely to be the development of triptan agents for use in children. Most treatments have only been evaluated in 1 or 2 studies, which limits the generalizability of the findings.

We strongly recommend performing a large, high-quality randomized, controlled trial evaluating different symptomatic medications compared with each other or to placebo treatment. Favorable high-quality studies should be performed and reported according to the CONSORT statement. Clinical improvement of HA should be used as the primary outcome measure, but quality of life, days missed at school, and satisfaction of child or parents should also be used as an outcome measure in future studies. *Pediatrics* 2005;116:e295–e302. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-2742](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-2742); *migraine, children, symptomatic treatment, systematic review, clinical trials, medication*.

ABBREVIATIONS. RCT, randomized, controlled trial; CCT, clinical controlled trial; HA, headache; IHS, International Headache Society; RR, relative risk; CI, confidence interval; IV, intravenous.

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Migraine is an important clinical problem in school-aged children, with an estimated prevalence of 2.7% to 10%.<sup>1,2</sup> It is characterized by attacks of intense, throbbing, unilateral head pain, often accompanied by nausea, vomiting, photophobia, and phonophobia.<sup>3,4</sup>

Treatment of pediatric migraine includes an individually tailored regimen of both nonpharmacologic

and pharmacologic measures. Nonpharmacologic modalities include lifestyle adjustments (ie, sleep hygiene, dietary adjustment, or exercise program), reassurance, stress management, biofeedback, and other biobehavioral therapies. Pharmacologic interventions include the use of symptomatic medication such as analgesics (acetaminophen, ibuprofen), triptans (sumatriptan), and antiemetics (prochlorperazine) and the use of prophylactic medication. The mainstay of symptomatic treatment in children with migraine is intermittent oral or suppository analgesics, but there is no coherent body of evidence on symptomatic treatment of childhood migraine available.

Good-quality controlled trials preferably summarized in a systematic review form the basis for evidence-based treatment guidelines, which may improve the management and treatment of individual patients. One systematic review on triptans only for pediatric migraine has been performed.<sup>5</sup> Based on 4 randomized, controlled trials (RCTs), they found effectiveness with nasal-spray sumatriptan compared with placebo in acute pediatric migraine, whereas oral sumatriptan and rizatriptan were not clearly beneficial.<sup>5</sup> To study adverse events, open-label studies were also included.<sup>5</sup>

The objective of this review was to describe and assess the evidence from RCTs and clinical controlled trials (CCTs) concerning the efficacy and tolerability of symptomatic treatment of migraine in children.

## METHODS

### Search Strategy

We searched Medline, Embase, PsychInfo, Web of Science, and Cinahl from inception to June 2004 using the terms "migraine," "headache," "cephalgia," "cephalalgia," "child\*," "infant," "teenage," "adolescent," or "p(a)ediatric" together with the search strategy for identifying clinical trials described by Robinson and Dickerson.<sup>6</sup> The Cochrane Controlled Trials Register was searched using the words "migraine," "headache," "cephalgia," "cephalalgia," "child\*," "infant," "teenage," "adolescent," or "p(a)ediatric." Additional strategies for identifying trials included searching the reference lists of review articles and included studies.

### Study Selection

We selected only RCTs and CCTs including symptomatic pharmacologic medicine used in the management of migraine in children (<18 years old), with criteria designed to distinguish migraine from other types of headache (HA). The use of a specific set of diagnostic criteria (eg, International Headache Society [IHS]<sup>3</sup> and Ad Hoc Committee on the Classification of Headache<sup>7</sup>) was not required, but migraine diagnoses had to be based on at least some of the distinctive features of migraine.<sup>3,4</sup> Our outcome measures of interest were: HA intensity, frequency or duration, HA index, and overall improvement. Rescue medication was defined as additional medications (other than study medication) permitted in nonresponders, usually limited to the habitual medications a person uses for their migraine HA. When a protocol permitted the use of rescue medication before outcome measurement (2–6 hours), then the latest outcome assessment not confounded by the use of rescue medication was extracted. No language restriction was applied.

Two authors (L.D. and J.K.J.B.) independently screened titles and abstracts of studies identified by the literature search for eligibility. All potentially relevant studies were retrieved as full papers and then again independently reviewed by 2 authors (L.D. and J.K.J.B.). Any disagreements were resolved through consensus, when possible, or by arbitration of a third author (A.P.V.).

### Methodologic Quality and Data Extraction

Two authors (L.D. and J.K.J.B. or A.P.V.) independently assessed the methodologic quality of the included trials using the Delphi list.<sup>8</sup> The Delphi list is a generic criteria list developed by international consensus and consists of (1) randomization, (2) adequate allocation concealment, (3) groups similar at baseline, (4) specification of eligibility criteria, (5) blinding of outcome assessor, (6) blinding of care provider, (7) blinding of patient, (8) presentation of point estimates and measures of variability, and (9) intention-to-treat analysis. One extra item was added because it was found to be relevant for these studies: (10) withdrawal/dropout rate (>20% or selective dropout) unlikely to cause bias. The methodologic criteria were scored as yes (1), no (0), or don't know (0).

A quality score of each trial was computed by counting the number of positive scores. Any disagreements were resolved through consensus, when possible, or by arbitration of a third author (J.K.J.B. or A.P.V.).

Data extraction was performed by 1 author (L.D.) and checked by a second author (A.P.V.). Disagreements were resolved by consensus. Extracted information included (if available) demographic data, detailed description of the intervention and control (ie, dose given, study duration), outcome measures, and information on adverse effects.

### Data Analysis

We calculated relative risks (RRs) with 95% confidence intervals (CIs). We performed an available-case analysis (data reported), and if sufficient data were available, we also performed a worst-case analysis (ie, all dropouts are assumed to be nonresponders). Data are presented as treatment success, indicating that a RR > 1 represents a better outcome for the first mentioned intervention group.

In case of a crossover trial, we ideally would like to restrict our analysis to first-period data only or, in case of a sufficient washout period and no carryover effect, data of both periods could be combined. In this review we analyzed the crossover trials as if they were parallel-group trials, because none of them provided separate data of each treatment period or data concerning a carryover effect, which would otherwise lead to exclusion of most crossover trials.

Statistical pooling was performed in the case of clinical homogeneity. In parallel studies, when >1 comparison from the same study (ie, sumatriptan 5, 10, and 20 mg versus placebo) was used for the statistical pooling of sumatriptan versus placebo, the results from the placebo group were evenly spread out over the 3 comparisons, and the number of patients in the placebo group was divided by 3 to prevent triple counting (R.J.P.M. Scholten, PhD, Dutch Cochrane Centre, verbal communication, 2004).

A qualitative analysis was performed by using a rating system with levels of evidence.<sup>9</sup> The evidence was judged to be strong when multiple ( $\geq 2$ ) high-quality RCTs produced generally consistent findings. Results were considered consistent if  $\geq 75\%$  of the studies reported similar results on the same outcome measure. It was judged to be moderate when 1 high-quality RCT or multiple ( $\geq 2$ ) low-quality RCTs or CCTs produced generally consistent findings. Evidence was considered to be limited when only 1 low-quality RCT or CCT existed and conflicting if the findings of existing trials were inconsistent. No evidence was considered when no RCTs or CCTs were found or when the authors provide no sufficient data for analysis. We arbitrarily regarded trials with methodologic quality scores of  $\geq 6$  as of high quality.<sup>9</sup>

## RESULTS

### Search Results

The results of our search strategy are presented in Fig 1. In total, 9 RCTs and 1 CCT are included in this review.

### Description of Studies

Full details of the included studies are presented in Table 1.

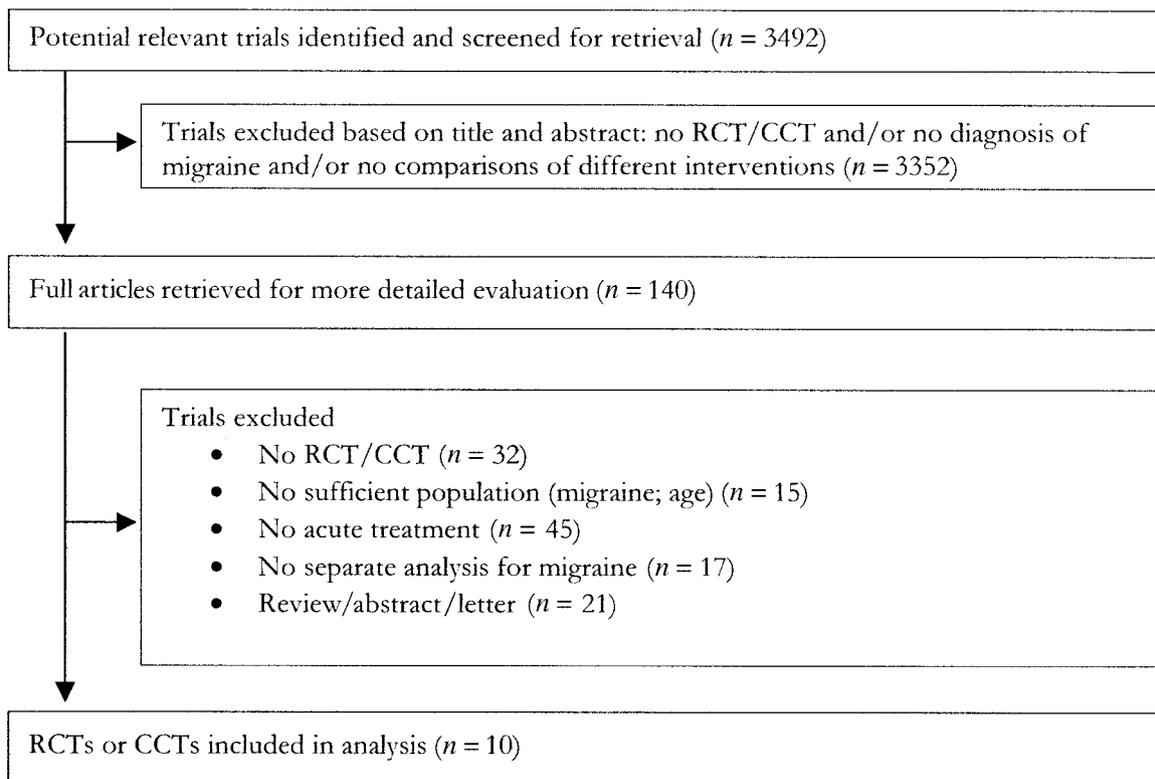


Fig 1. Flowchart showing results of the search strategy.

### Participants

The number of included participants in each trial ranged from 14 to 653 (mean  $158 \pm 201$  patients), with a total of 1575 patients included in this review. The mean percentage of participants who dropped out from the trials was 19.8% (range: 0–39.1%). Mean age of participants was  $11.7 \pm 2.2$  years (range: 4–18 years). Overall, the percentage of boys was generally the same as girls (mean: 55%; range: 42–82%). Nine of 10 trials used the criteria of the IHS to classify migraine, and 1 trial<sup>10</sup> used the criteria of Prensky and Sommer.<sup>11</sup> Six studies used a crossover design.

### Interventions

The pharmacologic interventions<sup>10,12–20</sup> used for symptomatic treatment could be divided into analgesic treatment and nonanalgesic treatment. Regarding oral analgesic treatment, the effectiveness of acetaminophen, ibuprofen, and nimesulide was evaluated. Regarding the nonanalgesic interventions, nasal-spray sumatriptan, oral sumatriptan, oral rizatriptan, oral dihydroergotamine, intravenous (IV) prochlorperazine, and IV ketorolac were evaluated. Eight studies included a placebo comparison.

### Outcome Measures

All studies used HA diaries to assess outcomes. Using this diary, among others, the frequency, intensity, and duration of HAs were scored on a Likert scale. In most studies a measure of clinical improvement was calculated. Improvement often was regarded as being clinically relevant when the patients' HAs decline by  $\geq 50\%$ . This score is presented as "HA clinical improvement" in Table 1 and is our

primary outcome measure. Other outcome measures were HA index, frequency, intensity or duration, rescue medication, and adverse events posttreatment and at follow-up.

### Methodologic Quality

Quality scores (with positive items in parentheses) are presented in the "study quality" section of Table 1. The median score for methodologic quality was 6 (range: 3–9). Using a cutoff point of 6 of 10 criteria, 6 studies (60.0%) were considered to be of high quality.<sup>10,12,13,16,18–20</sup> Most prevalent methodologic shortcomings were a concealed randomization method (unclear: 80%), the intention-to-treat analysis (unclear: 50%; negative: 20%), and comparability of groups at baseline (unclear: 70%; negative: 10%).

### Effectiveness of Symptomatic Treatment

Table 2 gives an overview of effect estimates of the different treatment modalities described below.

#### Oral Analgesic Treatment

##### Acetaminophen Versus Placebo

One high-quality study compared 15 mg/kg acetaminophen with placebo.<sup>12</sup> HA improvement was significantly higher for acetaminophen, although the use of rescue medication as well as the number of adverse events were not significantly different between the 2 groups. Adverse events mentioned for acetaminophen versus placebo were nausea (2.4% vs 3.7%) and vomiting (2.4% vs 7.4%).

##### Ibuprofen Versus Placebo

Two studies compared 10 mg/kg ibuprofen with placebo, including 1 high-quality study<sup>12</sup> and 1 low-

**TABLE 1.** Study Characteristics of Included Studies (Available From Authors or Published Electronically on Web Site of the Journal)

Study	Migraine Criteria Set	Participants	Interventions	Outcome Measures	Results*
Ahonen et al <sup>16</sup> ; RCT-crossover; QS: 6 (items 1 and 4-8)	IHS	45.7% female; mean age: 12.4 y (SD: 2.4 y); n = 129; 42 dropouts; time since onset of HAs: 3.8 y (range: 0.5-13.5 y)	I: sumatriptan nasal spray (10 mg with 20-39 kg [N = 31] and 20 mg with ≥40 kg body weight [N = 63] for 1 attack); N = 129; 39 dropouts C: placebo nasal spray (1 attack); N = 129; 42 dropouts MT: before and 15, 30, and 60 min thereafter, continuing hourly for up to 7 h unless child fell asleep or symptoms resolved Rescue medication: nonsteroidal anti-inflammatory drugs or acetaminophen 2 h after intake of study drug	HA diary (5-point Likert scale) HA improvement	HA clinical improvement: 1 h I vs C RR: 1.86 (1.27, 2.72); 2 h I vs C RR: 1.76 (1.29, 2.39)  Rescue medication: I vs C RR: 0.64 (0.44, 0.92) Adverse events: I vs C RR: 4.83 (2.27, 10.29)
Brousseau et al <sup>10</sup> ; RCT-parallel group; QS: 9 (items 1-8 and 10)	Premsky and Sommer	58.1% female; mean age: 13.7 y (range: 7.3-18 y); n = 62; no dropouts; time since onset of HAs: not stated	I: IV prochlorperazine (0.15 mg/kg [max: 10 mg] + 10 mL/kg bolus of normal saline solution for 1 attack); N = 33 C: IV ketorolac (0.5 mg/kg [max: 30 mg] + 10 mL/kg bolus of normal saline solution for 1 attack); N = 29 MT: before and 30 and 60 min thereafter	HA diary (Faces pain scale) HA improvement	HA clinical improvement: 60 min; I vs C RR: 1.54 (1.07, 2.20)  Adverse events: I vs C RR: 0.88 (0.06, 13.4)
Hämäläinen et al <sup>12</sup> ; RCT-crossover; QS: 7 (items 1 and 4-9)	IHS	50% female; mean age: 10.7 y (range: 4-15.8 y); n = 106; 28 dropouts; median time since onset of HAs: 2.83 y (range: 0.2-12.1 y)	I: acetaminophen (15 mg/kg for 1 attack); N = 106; 26 dropouts C1: ibuprofen (10 mg/kg for 1 attack); N = 106; 28 dropouts C2: placebo medication (cellulose for 1 attack); N = 106; 28 dropouts	HA diary (5-point Likert scale or visual analogue scale) HA improvement Rescue medication	HA clinical improvement: 2 h I vs C1 RR: 0.93 (0.70, 1.24); I vs C2 RR: 1.46 (1.02, 2.10); C1 vs C2 RR: 1.57 (1.10, 2.24) Rescue medication: <2 h I vs C1 RR: 0.98 (0.33, 2.89); I vs C2 RR: 0.73 (0.27, 2.01); C1 vs C2 RR: 0.75 (0.27, 2.06); ≥2 h I vs C1 RR: 3.41 (0.73, 15.9); I vs C2 RR: 0.68 (0.27, 1.70); C1 vs C2 RR: 0.20 (0.05, 0.88) Adverse events: I vs C1 RR: 0.49 (0.15, 1.56); I vs C2 RR: 0.43 (0.14, 1.35); C1 vs C2 RR: 0.89 (0.36, 2.19)
Hämäläinen et al <sup>18</sup> ; RCT-crossover; QS: 6 (items 1 and 4-8)	IHS	52.2% female; median age: 12.3 y (range: 8.3-16.4 y); n = 31; 8 dropouts; median time since onset of HAs: 3.4 y (range: 1.0-8.8 y)	Rescue medication: usual treatment within 2 h or >2 h after intake of study drug I: sumatriptan tablet (50 mg per 0.75-1.5 m <sup>2</sup> body surface area [6-12 y] or 100 mg for ≥1.5 m <sup>2</sup> body surface area [>12 y] for 1 attack); N = 31; 8 dropouts C: placebo medication. 1 attack, N = 31, 8 dropouts MT: before and 30 and 60 min thereafter, continuing hourly for up to 5 h unless child fell asleep or symptoms resolved Rescue medication: usual treatment after intake of study drug I: dihydroergotamine (20 µg/kg [or 40 µg/kg by no response] for 1 attack); N = 16; 4 dropouts C: placebo medication (1 attack); N = 16; 3 dropouts	HA diary (5-point Likert scale or visual analogue scale), resulting in pain intensity difference and summed pain intensity HA improvement Rescue medication Adverse events	HA clinical improvement: 2 h I vs C RR: 1.40 (0.52, 3.77)  Rescue medication: 1-2 h I vs C RR: 2.00 (0.81, 4.94) Adverse events: I vs C RR: 2.67 (0.81, 8.80) HA clinical improvement: 2 h I vs C RR: 3.79 (0.97, 14.8)
Hämäläinen et al <sup>20</sup> ; RCT-crossover; QS: 7 (items 1, 4-8, and 10)	IHS	38.5% female; mean age: 10.2 y (SD: 3.2 y); n = 16; 4 dropouts; median time since onset of HAs: 3.4 y	Rescue medication: usual treatment within 2 h or >2 h after intake of study drug I: sumatriptan tablet (50 mg per 0.75-1.5 m <sup>2</sup> body surface area [6-12 y] or 100 mg for ≥1.5 m <sup>2</sup> body surface area [>12 y] for 1 attack); N = 31; 8 dropouts C: placebo medication (1 attack); N = 16; 3 dropouts	HA diary (5-point Likert scale) HA improvement	HA clinical improvement: 2 h I vs C RR: 3.79 (0.97, 14.8)

**TABLE 1.** Continued

Study	Migraine Criteria Set	Participants	Interventions	Outcome Measures	Results*
Lewis et al <sup>14</sup> ; RCT-parallel group; QS: 4 (items 1, 5, 7, and 8)	IHS	44% (I) and 38.5% (C) female; mean age: 9.1 y (range: 6-12 y); <i>n</i> = 138; 54 dropouts; time since onset of HAs: not stated	MT: before and 30 and 60 min thereafter, continuing hourly for up to 5 h unless child fell asleep or symptoms resolved Rescue medication: usual treatment after intake of study drug  I: ibuprofen (7.5 mg/kg liquid for 1 attack); <i>N</i> = 45 C: placebo medication (1 attack); <i>N</i> = 39 MT: before and 30, 60, and 90 min thereafter, continuing hourly for up to 4 h unless child fell asleep or symptoms resolved Rescue medication: usual treatment after intake of study drug	Rescue medication  Adverse events  HA diary (4-point Likert scale) HA improvement Rescue medication	Rescue medication: 1-2 h I vs C RR: 1.08 (0.41, 2.83) Adverse events: I vs C RR: 2.17 (0.22, 20.94) HA clinical improvement: 2 h I vs C RR: 1.40 (1.00, 1.96)  Rescue medication: 2 h I vs C RR: 0.06 (0.01, 0.42)
Soriani et al <sup>15</sup> ; CCT-crossover; QS: 3 (items 4, 8, and 10)	IHS	50% female; mean age: 12.8 y (SD: 3.1 y); <i>n</i> = 66; 6 dropouts; time since onset of HAs: not stated	I: acetaminophen (15 mg/kg for 10 attacks); <i>N</i> = 66; 6 dropouts (300 attacks) C: nimesulide (2.5 mg/kg for 10 attacks); <i>N</i> = 66; 6 dropouts (300 attacks) MT: before and 90 min thereafter unless child fell asleep or symptoms resolved	HA improvement  Adverse events	HA clinical improvement: 1.5 h I vs C RR: 0.97 (0.89, 1.06) Adverse events: I vs C RR: 1.25 (0.35, 4.43)
Ueberall and Wenzel <sup>17</sup> ; RCT-crossover; QS: 5 (items 1, 4, and 8-10)	IHS	50% female; mean age: 8.1 (I) and 8.3 (C) y (range: 6.4-9.8 y); <i>n</i> = 14; no dropouts; median time since onset of HAs: 1.1 y (range: 0.8-2 y)	I: sumatriptan nasal spray (20 mg per dose for 1 attack); <i>N</i> = 14 C: placebo nasal spray (0.9% sodium chloride for 1 attack); <i>N</i> = 14 MT: before and 30 and 60 min thereafter, continuing hourly for up to 5 h unless child fell asleep or symptoms resolved	HA diary (4-point Likert scale) HA improvement  Rescue medication	HA clinical improvement: 2 h I vs C RR: 2.00 (1.05, 3.80)  Rescue medication: 1-2 h I vs C RR: 2.00 (0.81, 4.94)
Winner et al <sup>13</sup> ; RCT-parallel group; QS: 8 (items 1-8)	IHS	51.5% female; mean age: 14.1 y (SD: 1.6 y); <i>n</i> = 653; 143 dropouts; time since onset of HAs: not stated	I: sumatriptan nasal spray (5 mg per dose for 1 attack); <i>N</i> = 128 C1: sumatriptan nasal spray (10 mg per dose for 1 attack); <i>N</i> = 133  C2: sumatriptan nasal spray (20 mg per dose for 1 attack); <i>N</i> = 118  C3: placebo nasal spray (1 attack); <i>N</i> = 131 MT: before and 15, 30, 60, and 120 min thereafter	Rescue medication  HA diary (4-point Likert scale) HA improvement  Rescue medication  Adverse events	HA clinical improvement: 2 h I vs C1 RR: 1.03 (0.87, 1.24); I vs C2 RR: 1.05 (0.87, 1.26); I vs C3 RR: 1.26 (1.02, 1.54); C1 vs C2 RR: 1.01 (0.84, 1.22); C1 vs C3 RR: 1.21 (0.99, 1.49); C2 vs C3 RR: 1.20 (0.97, 1.49) Rescue medication: I vs C1 RR: 0.97 (0.61, 1.54); I vs C2 RR: 0.80 (0.51, 1.26); I vs C3 RR: 0.64 (0.42, 0.97); C1 vs C2 RR: 0.83 (0.53, 1.29); C1 vs C3 RR: 0.66 (0.44, 1.00); C2 vs C3 RR: 0.80 (0.54, 1.18) Adverse events: I vs C1 RR: 0.92 (0.67, 1.26); I vs C2 RR: 0.88 (0.64, 1.22); I vs C3 RR: 1.96 (1.26, 3.03); C1 vs C2 RR: 0.96 (0.71, 1.31); C1 vs C3 RR: 2.13 (1.39, 3.28); C2 vs C3 RR: 2.22 (1.44, 3.41)

TABLE 1. Continued

Study	Migraine Criteria Set	Participants	Interventions	Outcome Measures	Results*
Winner et al <sup>19</sup> ; RCT-parallel group; QS: 5 (items 1, 3, and 8-10)	IHS	N = 360; N completed: 296 18.2% female; mean age: 14 y; time since onset of HAs: not stated	I: rizatriptan (5 mg per dose for 3 attacks); N = 149 C: placebo medication (3 attacks); N = 147 MT: before and 30, 60, and 90 min thereafter, continuing hourly for up to 4 h unless child fell asleep or symptoms resolved Rescue medication: usual treatment >2 h after intake of study drug	HA diary (4-point Likert scale) HA improvement Rescue medication Adverse events	HA clinical improvement: 2 h I vs C RR: 1.18 (0.98, 1.42) Rescue medication: I vs C RR: 0.84 (0.64, 1.10) Adverse events: I vs C RR: 0.95 (0.69, 1.30)

C1 indicates control 1; C2, control 2; C3, control 3; I, intervention; MT, measure time; N, number of subjects who completed the trial; ns, not significant; QS, quality score on Delphi list, with positive items in parentheses.

\* Shown are standard mean differences with 95% confidence intervals (in parentheses).

quality study.<sup>14</sup> In the pooled analysis, HA improvement was significantly higher for ibuprofen, and the use of rescue medication was significantly higher for placebo. No difference in the number of adverse events was found (vomiting: 4.9% vs 7.4%; nausea: 3.7% for both; gastric pain: 1.2% [ibuprofen only]).<sup>12</sup>

#### Acetaminophen Versus Ibuprofen

One high-quality study compared 15 mg/kg acetaminophen with 10 mg/kg ibuprofen and found no significant differences for any outcome measures.<sup>12</sup>

#### Acetaminophen Versus Nimesulide

One low-quality study compared 15 mg/kg acetaminophen with 2.5 mg/kg nimesulide and found no significant differences.<sup>15</sup> Adverse events (mild abdominal discomfort and nausea) accompanied 9% of the treatments with acetaminophen and 6% of treatments with nimesulide.

We conclude that there is moderate evidence that both acetaminophen and ibuprofen are more effective in reduction of symptoms 1 and 2 hours after intake than placebo, with minor adverse effects. No clear differences in effect were found between acetaminophen and ibuprofen or nimesulide.

#### Triptans

##### Sumatriptan Versus Placebo

Four studies compared sumatriptan and placebo, including 3 high-quality studies<sup>13,16,18</sup> and 1 low-quality study.<sup>17</sup>

Three studies evaluated intranasal sumatriptan.<sup>13,16,17</sup> Ahonen et al<sup>16</sup> did not present outcomes for the doses separately. At 1 and 2 hours after administration we found significant differences concerning HA improvement in favor of sumatriptan. The use of rescue medication was significantly more for placebo, whereas the number of adverse events was significantly more for sumatriptan. Adverse events mentioned for sumatriptan versus placebo included bad taste (25.7% vs 3.1%), nausea (7.9% vs 8.3%), vomiting (3.9% vs 4.4%), triptan sensation (temperature [warmth], burning/stinging sensations, or paresthesia) (2.4% vs 1.6%), feeling of lightheadedness (2.2%, sumatriptan only), and stiffness in the jaw (1.1%, sumatriptan only).

One high-quality study evaluated oral sumatriptan and found no significant differences for any outcome measures.<sup>18</sup> Adverse events mentioned for sumatriptan were vomiting (17.4%), nausea (8.7%), dizziness (4.3%), and very strong photophobia (4.3%). For placebo, the adverse events were vomiting (8.7%) and nausea (4.3%).

##### Rizatriptan Versus Placebo

One low-quality study<sup>19</sup> compared oral rizatriptan with placebo and found no significant differences for clinical improvement of HA, rescue medication, or the number of adverse events. Adverse events mentioned for rizatriptan versus placebo were dry mouth (4.7% vs 3.4%), dizziness (4.7% vs 4.8%), asthenia (3.4% vs 2.0%), nausea (2.7% vs 8.2%), and somnolence (2.7% vs 8.2%).

We conclude that there is moderate evidence that nasal-spray sumatriptan is more effective in the reduction of symptoms than placebo, but with signifi-

**TABLE 2.** Overview: Results of Symptomatic Treatment

Comparisons	Total Trials, <i>n</i>	HA Clinical Improvement 2 h After Intake, RR (95% CI)	Rescue Medication 2 h After Intake, RR (95% CI)	Number of Adverse Events, RR (95% CI)
<b>Analgesic treatment</b>				
Acetaminophen vs placebo	1 H	1.5 (1.0, 2.1)*	0.7 (0.3, 1.7)	0.4 (0.1, 1.4)
Ibuprofen vs placebo	1 H, 1 L	1.5 (1.2, 1.9)*	0.1 (0.0, 0.4)*	0.9 (0.4, 2.2)
Acetaminophen vs ibuprofen	1 H	0.9 (0.7, 1.2)	3.4 (0.7, 15.9)	0.5 (0.2, 1.6)
Acetaminophen vs nimesulide	1 L	1.0 (0.9, 1.1)	—	1.3 (0.4, 4.4)
<b>Triptans treatment</b>				
Sumatriptan nasal spray vs placebo	2 H, 1 L	1.4 (1.2, 1.7)*	0.7 (0.5, 0.8)*	2.5 (1.7, 3.7)*
Sumatriptan tablets vs placebo	1 H	1.4 (0.5, 3.8)	2.0 (0.8, 4.9)	2.7 (0.8, 8.8)
Rizatriptan vs placebo	1 L	1.2 (1.0, 1.4)	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)
<b>Other treatment</b>				
Dihydroergotamine vs placebo	1 H	3.8 (1.0, 14.8)	1.1 (0.4, 2.8)	2.2 (0.2, 20.9)
Prochlorperazine (IV) vs ketorolac (IV)	1 H	1.5 (1.1, 2.2)*	—	0.9 (0.1, 13.4)

H indicates high-quality trial; L, low-quality trial; *n*, number of trials, which can have >1 comparison; —, no data available.

\* Significant difference.

cantly more adverse events. No differences in effect were found between oral triptans and placebo.

#### Other Medications

##### *Dihydroergotamine Versus Placebo*

One high-quality study compared oral dihydroergotamine with placebo.<sup>20</sup> We found no significant differences for clinical improvement of HA, rescue medication, or the number of adverse events, probably because of statistically low power (smallest treatment group: <25 patients). The 1 adverse event mentioned for dihydroergotamine versus placebo was vomiting (16.7% vs 7.7%).

##### *Prochlorperazine Versus Ketorolac*

One high-quality study compared IV prochlorperazine with IV ketorolac.<sup>10</sup> After 1 hour, prochlorperazine worked significantly better compared with ketorolac. The number of adverse events was not significantly different between the 2 groups.

We conclude that there is moderate evidence that IV prochlorperazine is more effective than IV ketorolac in the reduction of symptoms 1 hour after intake. No differences in effect were found between oral dihydroergotamine and placebo.

#### Worst-Case Analysis

When sufficient data were available, a worst-case analysis was conducted in which all dropouts were assumed to be nonresponders. Only 4 studies provided sufficient data to allow a worst-case analysis, but the overall conclusions did not change.<sup>12,16,18,20</sup>

### DISCUSSION

The most effective therapies for migraine are those that can be given quickly at the beginning of an attack and have a rapid onset of action. Based on the available literature, we conclude that over-the-counter analgesics such as acetaminophen and ibuprofen are relatively safe and effective. Most RRs were at ~1.5, which means that there is 50% more chance (risk) to recover when using, for example, ibuprofen instead of placebo. No clear differences in effect were found between the different analgesics. After finishing our study, another systematic review on treatments of pediatric migraine was published with similar conclusions.<sup>21</sup> This review included just

5 controlled trials on pharmacologic treatment, and no statistical pooling resulting in an overall effect estimate was performed.

The new frontier for symptomatic treatment is likely to be the development of triptan agents for use in children. We found moderate evidence that nasal-spray sumatriptan is more effective than placebo, but no differences in effect were found between oral sumatriptan and rizatriptan compared with placebo. It is possible that oral triptans may not be effective in children during acute migraine attacks because of nausea and vomiting. In adults, sumatriptan pharmacokinetic data have been collected after oral administration in patients suffering from migraine: the absorption from an oral tablet was delayed during a migraine attack because of gastric stasis, nausea, and vomiting.<sup>22</sup> It is likely that this also takes place in children.

Also, migraine attacks in children tend to be shorter than those in adults and may spontaneously remit within 2 hours. Medications, which would be anticipated to provide maximum benefit close to 2 hours after administration, may not show efficacy for shorter-duration attacks, and results may be comparable to those when using placebos.

Nasal administration offers an advantage over the tablet administration, because it provides faster absorption immediately after dosing, which results in faster initial relief of migraine symptoms. The only disadvantage of the use of nasal-spray sumatriptan compared with the other investigated medications is the adverse events. Although all reported adverse events were minor for all reported medications, the use of nasal-spray sumatriptan resulted in significantly more adverse events than the use of placebo.

Although systematic reviews offer the least biased method of summarizing research literature, our results must be interpreted with consideration of the quality of evidence from which they were obtained. None of the crossover trials provided separate data of each treatment period or data concerning the existence of a carryover effect. Positive results of analgesics and triptans in children and adolescents have frequently emerged from open-label studies, which might be biased.

Most treatments have been evaluated in only 1 or

2 studies, which limits the generalizability of the findings. There are no clinical trials that tested the efficacy of different triptans with each other. Studies comparing the efficacy of triptans to analgesic drugs with known efficacy are also needed.

Clinical improvement of HA and adverse events are 2 outcome measures frequently used in the included trials for symptomatic treatment of migraine attacks. Although most studies described the adverse events as mild and safe, the simple description of the kind and number of adverse events often gives insufficient insight into the severity and appreciation of the adverse events for a child. Outcome measures such as quality of life, satisfaction of child or parents, and days missed at school are not used.

We strongly recommend performing a large high-quality RCT that evaluates different symptomatic medications compared with each other or to placebo treatment. Favorable high-quality studies should be performed and reported according to the CONSORT statement (see [www.consort-statement.org](http://www.consort-statement.org)). Clinical improvement of HA should be used as the primary outcome measure, but quality of life, days missed at school, and satisfaction of child or parents should also be used as outcome measures in future studies.

### CONCLUSIONS

There is moderate evidence that analgesics (acetaminophen and ibuprofen) and nasal-spray sumatriptan are more effective than placebo treatment. Based on the available literature, no differences in effect were found between the different analgesics.

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