

## Overview of diagnosis and management of paediatric headache. Part II: therapeutic management

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**Abstract** A thorough evaluation of headache in children and adolescents is necessary to make the correct diagnosis and initiate treatment. In part I of this article (Özge et al. in *J Headache Pain*, 2010), we reviewed the diagnosis of headache in children and adolescents. In the present part, we will discuss therapeutic management of primary headaches. An appropriate management requires an individually tailored strategy giving due consideration to both non-pharmacological and pharmacological measures. Non-pharmacological treatments include relaxation training, biofeedback training, cognitive-behavioural therapy, different psychotherapeutic approaches or combinations of these treatments. The data supporting the effectiveness of these therapies are less clear-cut in children than in adults, but that is also true for the data

supporting medical treatment. Management of migraine and TTH should include strategies relating to daily living activities, family relationships, school, friends and leisure time activities. In the pharmacological treatment age and gender of children, headache diagnosis, comorbidities and side effects of medication must be considered. The goal of symptomatic treatment should be a quick response with return to normal activity and without relapse. The drug should be taken as early as possible and in the appropriate dosage. Supplementary measures such as rest in a quiet, darkened room is recommended. Pharmacoprophylaxis is only indicated if lifestyle modification and non-pharmacological prophylaxis alone are not effective. Although many prophylactic medications have been tried in paediatric migraine, there are only a few medications that have been studied in controlled trials. Multidisciplinary treatment is an effective strategy for children and adolescents with improvement of multiple outcome variants including frequency and severity of headache and school days missed because of headache. As a growing problem both children and families should be informed about medication overuse and the children's drug-taking should be checked.

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Non-pharmacological treatment

### Introduction

Headache is the most common complaint in children and adolescents. The incidence of childhood migraine and frequent headache has substantially increased over the past 30 years. The increased incidence is alarming and may be secondary to lifestyle changes but also due to increased

awareness of the disease in this age group. Primary headache (especially migraine and tension type headache, TTH) is the most important cause of headaches in this age group. In part 1 of this article [1] we reviewed the diagnosis of headache in children and adolescents. In the present part, we will discuss therapeutic management.

## Management of headaches

The general principles of management of headache in children and adolescents can be summarized as follows:

- Establish the diagnosis.
- Look for possible somatic and psychiatric comorbidities [2–6].
- Ask for triggers and assess degree of disability.
- Educate the child and family about the condition.
- Use a headache calendar to establish the characteristics of headache and associated symptoms.
- Establish realistic expectations and set appropriate goals.
- Discuss the expected benefits of pharmacological and non-pharmacological therapy and the time course to achieve them.
- Reduce the emotional mechanisms (on a personal level, within the family and at school) that provoke stress and may favour headache attacks.
- Advise to maintain a sound rhythm in daily life, which includes regular meals, sufficient fluid intake, physical exercise and sleep.
- Advise how to cope with trigger factors.

An algorithm for the diagnostic and therapeutic management of migraine is shown in Fig. 1.

### Non-pharmacological treatments

#### *Non-pharmacological treatment of migraine*

Behavioural interventions, particularly biofeedback and relaxation therapy have demonstrated their effectiveness in the treatment of both adults and older children with migraine in controlled trials. The physiological basis for their effectiveness is unclear, but data from one trial suggest that levels of plasma beta-endorphin can be altered by relaxation and biofeedback therapies. The data supporting the effectiveness of behavioural therapies are less clear-cut in children than in adults, but that is also true for the data supporting medical treatment. This is due in part to methodological issues, especially the lack of specific tests for migraine, which has hampered research and helped leading to an inappropriate de-emphasis on care for childhood headache. In addition, migraine headaches in

children are often briefer and have a higher rate of spontaneous remission than those experienced by adults, making it difficult to separate effective from ineffective treatments [7–9].

Starting from the consideration that children and adolescents with headache show greater indices of psychopathology [10–14] and show higher risk of developing psychological disorders in adulthood than healthy controls [15], different psychotherapeutic approaches are sometimes provided in clinical practice. Relaxation and cognitive-behavioural techniques have been found to reduce the intensity and frequency of headache in children and adolescents [16, 17].

Prospective, randomized, partly double-blind, placebo-controlled, parallel-group trial showed that Butterbur root extract and music therapy might be superior to placebo and may represent promising treatment approaches in the prophylaxis of paediatric migraine [18].

The specialists involved in the assessment and care of headache patients should strive to increase their knowledge of alternative therapies, so as to be better equipped to guide patients towards safe, economical and potentially effective treatments, rather than useless, costly or dangerous ones.

#### *Non-pharmacological treatment of TTH*

Behavioural headache treatments include relaxation training, biofeedback training, cognitive-behavioural therapy or combinations of these treatments. Among behavioural headache treatments, the two most common types of biofeedback for headache have been electromyographic biofeedback for TTH and “handwarming” or thermal biofeedback for migraine [9, 19–22]. Magnesium salt seems to be effective in treating the paediatric episodic and chronic TTH (ETTH, CTTH), but further well-controlled studies are needed [23].

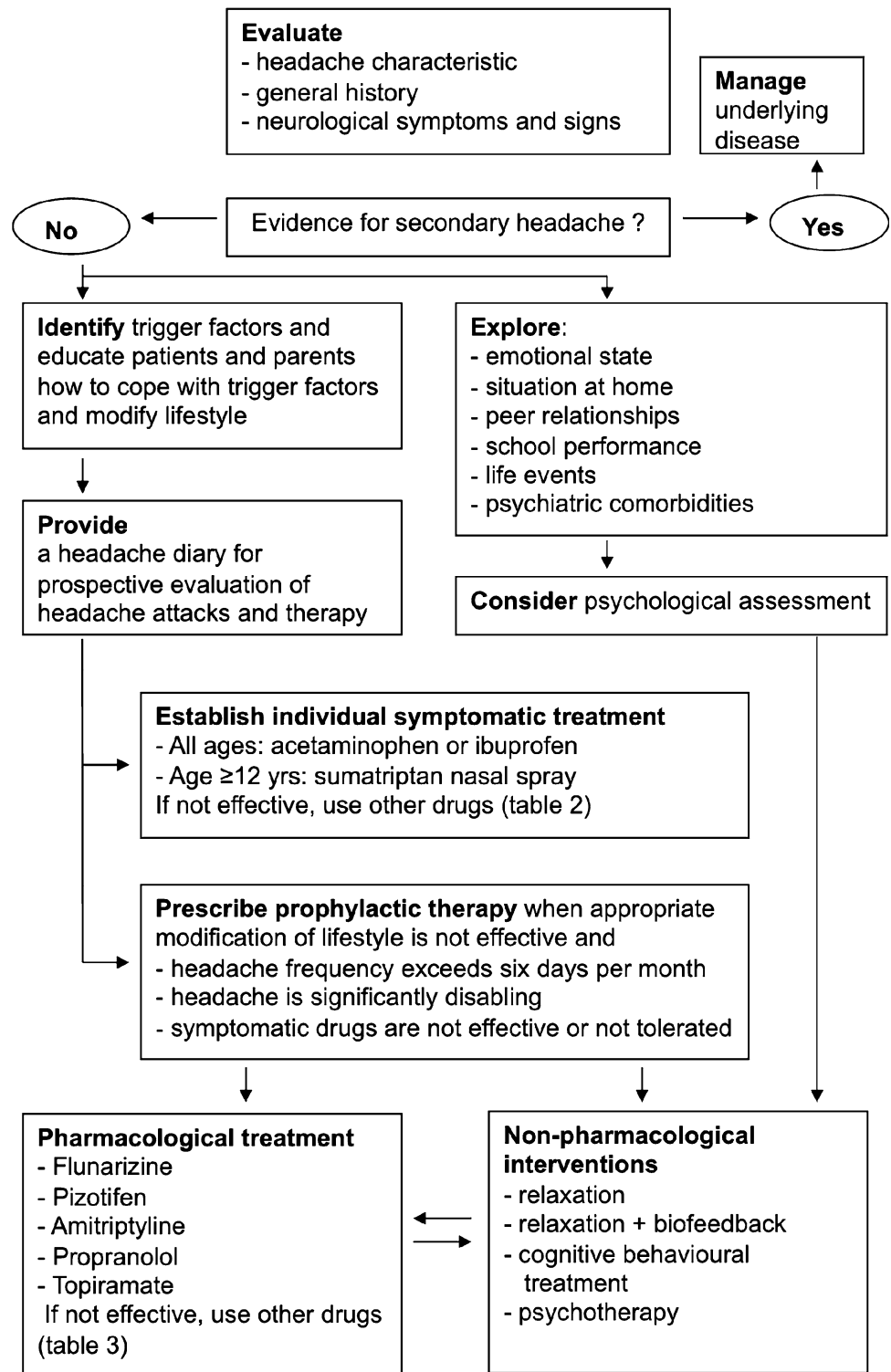
There are restricted data about the natural history of childhood and adolescent TTH. It is accepted that over than 50% of the sufferers improve with a comprehensive headache managements. The most important predictors of prognosis are comorbid medical and psychological conditions and family problems [24, 25].

### Pharmacological treatments

#### *Pharmacological treatment of migraine*

The data on efficacy and safety of medications in children are limited. Therefore, it may be necessary to use medications off label strictly weighing up the benefits and risks. However, medications which have shown efficacy in adults must not be used routinely in younger patients (please refer to Ref. [26]). Only few randomized placebo-controlled

**Fig. 1** Algorithm for the diagnostic and therapeutic management of migraine



clinical trials have been conducted in paediatric headache patients for both acute and preventive drugs. Moreover, the few published studies show a high placebo response rate in children, up to 55% for prophylactic drugs, up to 69% for symptomatic ones. Such high placebo response rates drastically reduce the possibility to find effective agents

(in terms of statistically significant superiority over placebo) and may lower the interest of pharmaceutical companies and independent researchers to perform new clinical trials in this field. On the other hand, the placebo effect is a psychobiological phenomenon that can be attributed to different mechanisms [27]; it should be properly used by

the physician, simply bearing in mind that any medical treatment is surrounded by a psychosocial context that affects the therapeutic outcome.

The pharmacological treatment of migraine consists of symptomatic and/or prophylactic therapy. The former is aimed at relieving or ameliorating the symptoms of an acute attack, whereas prophylactic therapy, which requires the daily intake of medication for a certain period of time, decreases the frequency of the attacks and the severity of pain.

**Symptomatic drug treatment** The goal of treatment should be a quick response with return to normal activity and without relapse. Several key concepts should be made known to patients. Medication use should be limited to avoid medication overuse headache. It is important that an appropriate dose is used. Medications should be taken shortly after onset of migraine headache to optimize the effect, even though scientific evidence supporting this recommendation is lacking. The medication should be available to the patients also at school. Allodynia during a migraine in adults correlates with response to treatment of acute migraine with triptans and the progressive nature of migraine. This has emphasized the importance of early recognition of headache and appropriate treatment. Allodynia has recently been shown to be present in 37% of children during their migraine. Allodynia is often not routinely evaluated during a headache history even though there may be potential therapeutic implications. Prominent scalp symptoms include sensitivity to touch and difficulty brushing hair [28–30].

The available efficacy data about symptomatic drugs [31–46] are summarized in Tables 1 and 2. The following findings should be kept in mind:

- At 1 h acetaminophen tended to be slightly more effective (39% of children relieved) than ibuprofen (37% of children relieved), but 2 h after administration ibuprofen was more effective (68 vs. 54%).
- Sumatriptan nasal spray was superior to placebo and was well tolerated. No serious adverse events occurred with taste disturbance as the most common one.
- Pain relief at 2 h was achieved in significantly more attacks treated with rizatriptan 5-mg tablets (77%) or with rizatriptan 5-mg wafer (77%) than with standard care (64%).
- Pain relief rates after 2 h were 28% for placebo, 62% for zolmitriptan and 69% for ibuprofen (placebo vs. zolmitriptan  $p < 0.05$ ; placebo vs. ibuprofen  $p < 0.05$ ). Both drugs are well tolerated with only mild side effects.
- The Food Drug Administration has recently approved almotriptan for the acute treatment of migraine headache in adolescents. Nevertheless, almotriptan is still not approved in Europe.
- There are limited data about other triptans.

- In summary, 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 compounds.

There is a lack of studies addressing the question of treatment in the emergency department of children with migraine. Future studies should focus on finding the best first-line agent for mild to moderate attacks in the emergency department and to confirm the usefulness of prochlorperazine as treatment for severe attack or status migrainosus. In the latter studies, attention should be given to adverse drug reactions associated with prochlorperazine. Furthermore, treatment to decrease the recurrence of migraine attack and the need for rescue medications after discharge from the emergency department should also be carefully evaluated [30, 48].

**Prophylactic drug treatment** Pharmaco-prophylaxis is only indicated if lifestyle modification and non-pharmacological prophylaxis alone are not effective. Although many prophylactic medications have been tried in paediatric migraine, there are only a few medications that have been studied in controlled trials. Prophylactic medications are recommended only when migraines are occurring with sufficient frequency (usually 3–4 per month) and severity to impact a patient's daily function or quality of life (e.g. missing school). To minimize adverse effects, prophylactic medications are started at the lowest dose and titrated upward as needed. They have to give a through time period (at least 4–6 months), and both comorbidities and side effects of the drug have to be taken into consideration [30, 49].

Prophylactic drugs evaluated in placebo-controlled and open-label trials for migraine [50–71] have been summarized in Table 3. The following findings should be kept in mind:

- Flunarizine is an effective drug. Its use is limited by daytime sedation found in 10% of the patients and weight gain in more than 20%. Because of probable D2 receptor interaction it should not be given for more than 3 months (administering it in the early evening can avert daytime sleepiness, dosage 5 mg/die) [72, 73].
- Propranolol was found to be superior to placebo in one randomized controlled trial and not effective in two others. It was found to activate asthma in subjects with atopic disorders or a positive history of atopic disorders, and there are no follow-up studies concerning long-term risks of betablockers. Therefore, some centres do not use betablockers for migraine prophylaxis in children.
- The overall positive response rate of cyproheptadine was 83% and common side effects included sedation and increased appetite.

**Table 1** Symptomatic drugs for migraine management evaluated in placebo-controlled and open clinical trials

References	Drug	Study design	Evidence level	Dose	Age (years)	Number of patients	Responders (%)		p value
							Active drug	Placebo	
Hamalainen et al. [31]	Ibuprofen	RCT	A	10 mg/kg	4–16	88	68	37	<0.05
Lewis et al. [32]	Ibuprofen	RCT		7.5 mg/kg	6–12	84	76	53	0.006
Evers et al. [33]	Ibuprofen	RCT		200–400 mg	6–18	32	69	28	<0.05
Hamalainen [31]	Acetaminophen	RCT	B	15 mg/kg	4–16	88	54	37	<0.05
Hamalainen et al. [34]	Dihydroergotamine	RCT	C	20, 40 µg/kg	5–15	12	58	16	NS
Ueberall [35]	Sumatriptan nasal	RCT	A	20 mg	6–10	14	86	43	0.03
Winner et al. [36]	Sumatriptan nasal	RCT		5–10–20 mg	12–17	510	66 <sup>a</sup>	53	<0.05
Ahonen et al. [37]	Sumatriptan nasal	RCT		10–20 mg	8–17	83	64	39	0.003
Winner et al. [38]	Sumatriptan nasal	RCT		20 mg	12–17	738	61	52	NS
Hamalainen et al. [39]	Sumatriptan oral	RCT	C	50–100 mg	8–16	23	30	22	NS
Mac Donald [40]	Sumatriptan sc.	OT	C	3–6 mg	6–16	17	64	–	–
Linder [41]	Sumatriptan sc.	OT		0.06 mg/kg	6–18	50	78	–	–
Winner et al. [42]	Rizatriptan	RCT	C	5 mg	12–17	196	66	56	NS
Visser et al. [43]	Rizatriptan	RCT		5 mg	12–17	234	68	69	NS
Visser et al. [43]	Rizatriptan	OT		5 mg	12–17	686	77	–	–
Linder and Dowson [44]	Zolmitriptan oral	OT	C	2.5–5 mg	12–17	38	88–70	–	–
Evers et al. [33]	Zolmitriptan oral	RCT		2.5 mg	6–18	32	62	28	<0.05
Charles [45]	Almotriptan oral	OT	B	6.25–12.5 mg	11–17	15	86	–	–
Linder et al. [46]	Almotriptan oral	RCT		6.25–12.5–25 mg	12–17	866	67–73	55	<0.001

Evidence level: findings regarding symptomatic drugs were reviewed and the recommendations were categorized into different levels (A–C) [47]. Level A: two or more clinically controlled, randomized studies carried out according to good clinical practice (GCP), versus placebo or versus active treatment of proven efficacy. Level B: one clinically controlled, randomized study carried out according to GCP or more than one well-designed clinical case–control study or cohort study. Level C: favourable judgment of two-third of the Ad Hoc Committee members, historical controls, non-randomized studies, case reports

NS no statistically significant difference between active drug and placebo, RCT randomized controlled trial, OT open trial

<sup>a</sup> 5 mg

**Table 2** Summary of the efficacy of medication used to treat acute migraine attacks in children and adolescents [45]

	Outcome			
	Pain relief	Pain-free	Recurrence	Need for rescue medications
<b>Oral medication</b>				
Acetaminophen (n = 1)	+	–	–	–
DHE (n = 1)	–	–	–	–
Ibuprofen (n = 3)	+	±	–	±
Rizatriptan (n = 3)	±	–	–	±
Sumatriptan (n = 1)	–	±	–	–
Zolmitriptan (n = 2)	±	±	–	+
<b>Intranasal medication</b>				
Sumatriptan (n = 4)	±	±	–	±
<b>Intravenous medications</b>				
Prochlorperazine (n = 1)	+	?	–	?
Ketorolac (n = 1)*	?	?	?	? ±

+ studies showing consistent positive results or a study showing positive result; – studies showing consistent negative results or a study showing negative result; ± studies showing inconsistent results; ? not evaluated

\* Used as a comparative agent against prochlorperazine

**Table 3** Prophylactic drugs for migraine management evaluated in placebo-controlled and open clinical trials

References	Drug	Daily dose	Age in (years)	Number of patients	Study design	Evidence level	% responders or <i>p</i> values (*)
<b>Antihypertensive drugs</b>							
Ludvigsson [50]	Propranolol	60–120 mg	7–16	28	RCT	C	82 vs. 14%
Forsythe et al. [51]	Propranolol	80 mg	9–15	39	RCT		NS
Olness et al. [52]	Propranolol	3 mg/kg	6–12	28	RCT		NS
Sillampää [53]	Clonidine	25–50 µg	≤15	57	RCT	C	NS
Sills et al. [54]	Clonidine	0.07–0.1 mg	7–14	43	RCT		NS
<b>Calcium channel blockers</b>							
Guidetti et al. [55]	Flunarizine	5 mg	10–13	12	OT	A	66%
Sorge et al. [56]	Flunarizine	5 mg	5–11	63	RCT		<i>p</i> < 0.001 (HA frequency) <i>p</i> < 0.01 (HA duration)
Visudtibhan et al. [57]	Flunarizine	5–10 mg	7–15	21	OT		66%
Battistella et al. [58]	Nimodipine	10–20 mg	7–18	37	RCT	C	NS
<b>Serotonergic drugs</b>							
Gillies et al. [59]	Pizotifen	1–1.5 mg	7–14	47	RCT	C	NS
Lewis et al. [60]	Cyproheptadine	2–8 mg	3–12	30	OT	C	83%
<b>Antidepressants</b>							
Battistella et al. [61]	Trazodone	1 mg/kg	7–18	35	RCT	C	NS
Hershey et al. [62]	Amitriptyline	1 mg/kg	9–15	192	OT	C	80%
Lewis et al. [60]	Amitriptyline	10 mg	3–12	73	OT		89%
<b>Anticonvulsants</b>							
Caruso et al. [63]	Divalproex sodium	15–45 mg/kg	7–16	42	OT	B	76%
Sedaroglu et al. [64]	Divalproex sodium	500–1,000 mg	9–17	10	OT		<i>p</i> = 0.000 (HA severity) <i>p</i> = 0.002 (HA frequency) <i>p</i> = 0.001 (HADuration)
Hershey et al. [65]	Topiramate	1.4 ± 0.7 mg/kg	8–15	75	OT	A	<i>p</i> < 0.001 (HA frequency)
Winner et al. [66]	Topiramate	2–3 mg/kg	6–15	162	RCT		NS
Lewis et al. [67]	Topiramate	100 mg	12–17	103	RCT		72%
Miller [68]	Levetiracetam	250–1,500 mg	3–17	19	OT	B	<i>p</i> < 0.0001 (HA frequency)
Pekalnis et al. [69]	Levetiracetam	250–1,500 mg	6–17	20	OT		<i>p</i> < 0.0001 (HA frequency)
Belman et al. [70]	Gabapentin	15 mg/kg	6–17	18	OT	C	80%
Pakalnis and Kring [71]	Zonisamide	5.8 mg/kg	10–17	12	OT	C	66%

Evidence level: findings regarding symptomatic drugs were reviewed and the recommendations were categorized into different levels (A–C) [47]. Level A: two or more clinically controlled, randomized studies carried out according to good clinical practice (GCP), versus placebo or versus active treatment of proven efficacy. Level B: one clinically controlled, randomized study carried out according to GCP or more than one well-designed clinical case–control study or cohort study. Level C: favourable judgment of two-thirds of the Ad Hoc Committee members, historical controls, non-randomized studies, case reports

NS no statistically significant difference between active drug and placebo, HA headache, RCT randomized controlled trial, OT open trial

\* The % is expressed as overall % of responders (OT) or active-drug vs placebo % of responders (RCT); *p* values refer to active drug versus placebo comparisons (RCT) or pre-treatment versus post-treatment comparison of headache characteristics (OT)

- There are limited confirmative data about trazodone.
- Amitriptyline (1 mg/kg) is an effective drug with an 84.2–89% positive response rate and only mild sedation was reported as side effect.
- Divalproex sodium (15–45 mg/kg/day) is an effective drug with 50% headache reduction seen in 78.5% of patients, 75% reduction in 14.2% of patients, and 9.5% of patients became headache-free after 4 months of treatment. The observed side effects were dizziness, drowsiness and increase in appetite.
- Topiramate is an effective drug for the reduction of headache frequency, severity and duration. The most common side effects reported were cognitive (12.5%), weight loss (5.6%) and sensory (2.8%).
- There are limited data about levetiracetam, gabapentin and zonisamide.

### Pharmacological treatment of TTH

Most TTH is best managed by primary care. ETTH is self-limiting, but children and their parents generally consult doctors when headaches occur frequently and are no longer responsive to analgesics. Medication overuse can be a common problem in patients with frequent headache. The treatment of migraine and TTH overlaps. Both require acute treatment, either behavioural or pharmaceutical. Behavioural treatment is needed for all types of TTH. Preventive pharmaceutical treatment is needed for frequent TTH if lifestyle modification and non-pharmacological treatment alone are not effective. Although childhood TTH is often treated with medication, few studies have been published the efficacy of medication in paediatric TTH. More studies in children need to be done regarding the treatment of this common disorder. The lack of availability and cost of non-pharmacological interventions might diminish the use of some treatment modalities [74, 75].

For acute treatment of ETTH, paracetamol, aspirin and combination analgesics are effective and inexpensive drugs. Non-steroidal anti-inflammatory drugs are also effective first-line therapeutics for ETTH in adults. In children younger than 15 years, aspirin is not recommended because of the concern regarding Reye's syndrome. Paracetamol seems to be safe even in young children [75–78].

Frequent headaches in children and adolescents often require preventive management. Prophylactic pharmacological treatment should be considered in CTTH if non-pharmacological management is inadequate. For children with frequent headache, amitriptyline might be beneficial, although no placebo-controlled studies have been performed [62].

### Treatment of cluster headache

Several treatment alternatives have been tried in cases reported in the literature. According to these data, the most effective symptomatic treatments are oxygen [79–82], sumatriptan [81, 83] and acetylsalicylic acid [80–84]. Prophylactic treatments reported in literature are prednisone/prednisolone [85, 86], indomethacin [84], pizotifen [81], verapamil [81, 82, 87], methysergide [79, 83, 85], loratadine [88], astemizole [88] and flunarizine [89]. No controlled study has been reported.

If oxygen is administered at the onset of an attack via a non-rebreathing facial mask at a flow rate of at least 7 l/min, approximately 70% of patients will obtain pain relief within 15 min. This therapy has obvious practical limitations and requires oxygen being readily available at the patient's home [85, 90]. Considering the unbearable pain intensity, off-label use of sumatriptan nasal spray or

subcutaneous sumatriptan may be necessary. Ergotamine has also been used. It is not recommended for acute CH-treatment in children, but might be given in the evening for preventing night-time attacks. Children between 6 and 9 years of age should receive 0.1 mg/dose, those between 9 and 12 years of age should receive 0.5 mg, and those between 12 and 16 years of age should receive 0.75 mg/dose. Lidocaine applied with a spray bottle or by dropping in the nostril ipsilateral to pain achieves moderate pain relief, and it may be useful as an adjunctive therapy. Although the reason for steroid efficacy is unknown, the use of cortisone in the acute period can stop the attacks and may help to prevent further attacks. In adolescents a marked relief of cluster headache in 77% of 77 episodic cluster headache patients, and a partial relief in another 12% of patients treated with prednisone was reported [85, 90]. For prophylactic treatment the efficacy of verapamil has been attributed to a possible stabilization of vascular tone. It is generally well tolerated and can be used in combination with corticosteroids, sumatriptan and ergotamine [91, 92].

### Life quality of headaches

Health-related quality of life (QOL) is an emerging area of headache research with a direct impact on patient adherence, patient satisfaction and treatment effectiveness. On the other hand, the assessment of QOL in children is difficult, since measures must consider children's changing cognitive and social development [93, 94]. Data-based analyses revealed that children with frequent or severe headaches (FSH) were significantly more likely than those without FSH to exhibit high levels of emotional, conduct, inattention-hyperactivity, and peer problems and were significantly more likely than children without FSH to be upset or distressed by their difficulties and to have their difficulties interfere with home life, friendships, classroom learning and leisure activities [95]. Subjects familiar with headache experienced more stress, fatigue, depression, and somatic symptoms; they felt less strong, had a less cheerful mood and reported lower satisfaction with health and with life in general than the subjects who never had headaches [96]. The impact of headaches on QOL is similar to that found for other chronic illness conditions, with impairments in school and emotional functioning being the most prominent [97]. Headache is the third most common cause among illness-related causes of school absenteeism resulting in substantial impairment among paediatric patients [98]. A specific questionnaire (PedMIDAS) provides a tool to assess the impact of migraines in children and to monitor response to treatment. Further research should focus on additional validation of the PedMIDAS

using a larger population and sampling from other populations (e.g. primary care and community samples) [99].

## Conclusions

- Management of migraine and TTH should include strategies relating to daily living activities, family relationships, school, friends and leisure time activities.
- Management should be completed by education (both of the children and parents), non-pharmacological interventions and psychosocial support.
- With reference to symptomatic treatment, the drug should be taken as early as possible and in the appropriate dosage. In cases with early onset of nausea and/or vomiting endorectal or parenteral administration should be preferred. Antiemetic drugs should not be provided if the child vomits only once or headache stops after vomiting. If an antiemetic is required, ondansetron may be preferred for its good tolerability. Supplementary measures such as rest in a quiet, darkened room is recommended.
- Multidisciplinary treatment is an effective strategy for children and adolescents with improvement of multiple outcome variants including frequency and severity of headache and school days missed because of headache.
- In the pharmacological treatment age and gender of children, headache diagnosis, comorbidities, need and side effects of medication must be considered.
- As a growing problem both children and families should be informed about medication overuse and the children's drug-taking should be checked.
- Regular follow-up care is needed, especially for those children with more severe initial headache presentation.

**Conflict of interest** None.

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