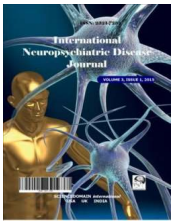

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Treatment of Primary Headaches in Paediatric Age: A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors IT and PAB carried out the literature review and drafted the manuscript. Authors IT, PAB, MN, MFP, DDC, SS and MG contributed to the critical revision of the manuscript for important intellectual content, editing and approval of final draft.

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ABSTRACT

Primary headaches have a high prevalence in paediatric age and may pose a high strain on the quality of life of young patients. Adequate care involves a patient-by-patient approach, and this generally relies both on bio-behavioural measures and on pharmacological and non-pharmacological interventions. We performed an updated review on acute and preventive pharmacological treatments for juvenile primary headaches emphasizing the efficacy and tolerability of the various molecules. Our literature review emphasized that most of the available information on paediatric primary headaches is derived from relatively low quality data; therefore, results should be considered with caution, and quality data from future large series should be warranted. With these limitations, in general there is broad agreement in considering analgesics and NSAIDs as first-line pharmacological treatments in the acute phase both for migraine and TTH in children. As regards migraine, other medications used for attacks may include antiemetics and triptans, whereas calcium-channel blockers, antihypertensive drugs, serotonin modulators, antidepressants and

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antiepileptics may be used for prophylaxys. Data are more limited as regards prophylaxis of paediatric TTH, though amitriptyline and magnesium have been used in these cases. Non pharmacological interventions may also provide useful in both headache types, as well as alternative therapies, also in view of their more favourable tolerability profile, and these therapies should be conjugated with more traditional medications to maximise the patient's benefit.

Keywords: Headache; paediatric primary headache; children; migraine; tension-type headache.

1. INTRODUCTION

Primary headaches have a high prevalence in paediatric age and specific therapeutic approaches, also taking into account comorbidities, should be reserved for different headache types. Primary headaches may pose a high strain on the quality of life of young patients. Adequate care involves a patient-by-patient approach, and this generally relies both on bio-behavioural measures (i.e. lifestyle changes, headache triggers avoidance), and on pharmacological and non-pharmacological interventions. Literature data on pharmacological approaches are still relatively limited and, even though in the case of migraine the improved knowledge on its pathogenesis has contributed to ameliorate its therapeutic management, data are scarcer and more fragmentary for paediatric tension-type headache.

In the clinical setting, the severity and disability imposed by headache need to be taken into account, and a patient-tailored approach based on pharmacological and non-pharmacological interventions (biofeedback, stress management copy, relaxation techniques, etc) should be adopted. The primary goals of treatment include: a) decrease of attack frequency, intensity and duration, and of therefore of the disability imposed by headache, b) improvement of the quality of life, c) prevention of escalation of pain-relief medications, d) reduction of stress relative to recurrent headache. Future studies on large cohorts, multi-centre trials, inclusion of patients from primary centres for headache care with adherence to the new diagnostic criteria ICHD-2013 [1] should be warranted. Besides, clinical improvement as well as newer parameters should be taken into account when assessing treatment efficacy, such as quality of life, missed days of school and patients' and parental perceived benefit.

2. MIGRAINE

Prevalence of migraine is high in paediatric age, with increasing trends from pre-school (3%) to school age (4-11%), peaking in adolescence (8-23%); differently to pre-school age, in teenagers prevalence is higher in females [2]. Despite representing an important condition in young patients, migraine is often under-diagnosed and under-recognised, resulting in marked disability and affecting quality of life, with high direct and indirect costs.

Guidelines on therapeutic approaches to migraine have been introduced in Italy [3] as well as in other European countries [4-8] and in the United States [9].

A key role in migraine management is universally recognised to counselling, through which the patient and their family are informed and reassured on the nature of the symptom. Taking a detailed patient's history allows identification and avoidance of possible trigger factors, for example unhealthy diet, poor sleep habits and excessive sedentary lifestyle. As regards diet, previous recommendations on avoidance of some food considered migraine triggers (i.e. chocolate, citrus fruit, additives, etc) have now been put into perspective.

Guidelines for migraine management [3-9] currently recommend an integrated approach including non-pharmacological interventions (healthy diet, exercise, rest stress-reduction strategies, acupuncture, biofeedback, relaxation techniques), pharmacological symptomatic treatments for the acute phase (which should be taken immediately after onset of pain), and pharmacological prophylactic treatment.

3. PHARMACOLOGIC TREATMENT OF MIGRAINE ATTACKS

Shared goals of all treatments include: a) pain relief and abolishment of associated symptoms; b) restoring full function; c) helping the patient improve headache management; d) minimizing side effects; e) avoiding pain recurrence; f) improving quality of life; g) avoiding excessive use of painkillers (which is a rarer occurrence in paediatric age compared to adults); h) reduction of stress related to recurring headache. When prescribing a medication, drug pharmacokinetics

and pharmacodynamics in paediatric age should be taken into account, as well as contraindications, side effects, and the cost-benefit profile of the drug itself. Monotherapy is generally preferable, with drug dose based on the patient's body weight. Symptomatic drugs are the mainstay of treatment in the patients who experience rare headache attacks (≤4 per month), or who have contraindications or poor compliance to prophylactic treatments [10-12]. Moreover, it should not be forgotten that the proportion of placebo-responders with symptomatic treatments is higher in young migraineurs (20-60%) than in adult patients (6-44%), making it more challenging to get significant results in controlled trials [13]. At the moment, data are still limited in paediatric age and results from controlled trials are reported in recent meta-analyses [9,14-17]. In the management of migraine attacks in paediatric age two groups of drugs should be taken into account, "non-specific" medications (including nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and/or anti-emetics), and treatments "specific" for migraine, represented by triptans [18].

4. ANALGESICS AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have been studied extensively in young patients with headache [9,14-16,19-22]. There is broad agreement in the literature and in the available guidelines [3-9] on the use of oral paracetamol (15 mg/kg) and of ibuprofen (7.5-10 mg/kg) from the first years of life. In the few available controlled trials, both these medications were significantly more effective than placebo, both in pain improvement after one hour from administration and in pain-freedom rates after two hours. Tolerability was good for both medications. Rare adverse events to paracetamol (skin rash, erythema, urticaria and pancythopaenia) and to ibuprofen (gastric pain, nausea, vomiting) should be borne in mind, as well as to both medications (drug hypersensitivity, hepatic failure, haemolytic anaemia). As regards other NSAIDs, there is only one open study comparing nimesulide (2.5 mg/kg) and paracetamol (15 mg/kg) in pubertal migraineurs, demonstrating similar efficacy (improvement in 50%, pain-freedom in 25%) and tolerability [23]. Table 1 details the dosage in paediatric age for different analgesic medications and NSAIDs, even though for most of them no controlled studies are available. Finally, it should not be forgotten that the frequent and prolonged use of these treatments (medication overuse) may favour headache chronicization, as demonstrated in a small case series of adolescent patients [24].

Table 1. Symptomatic treatment of migraine in paediatric age: Analgesics and NSAIDs

Medication	Age	Dose
Paracetamol*	No limitations	15 mg / kg
Ibuprofen*	> 6 months	7.5-10 mg/kg
Ketoprofen	> 6 years	1 - 2 mg/kg
Diclofenac	> 6 years	0.5 - 1 mg/kg
Piroxicam	> 6 years	10 - 20 mg
Naproxen sodium	> 16 years	250 mg
Acetilsalicilic acid	> 16 years	10 - 15 mg/kg
Indometacine	> 16 years	25 - 50 mg
Nimesulide*	> 18 years	1 - 2 mg/kg

** Controlled studies*

5. ERGOT-DERIVATIVES

Ergot-derivatives are no longer used in paediatric age due to their unfavourable tolerability profile, including emetic and vasocontrictive effects secondary to their action on multiple receptor sites.

6. ANTIEMETICS

Antiemetics (antidopaminergic) may be used for attacks associated with intense nausea or vomiting; therefore, rectal or intravenous administration are the preferred routes. In the past, rectal promethazine (25-50 mg) has been used, whereas more recently other drugs have been introduced, like metoclopramide and/or prochlorperazine maleate; these medications should be used with caution due to the possibility of extrapyramidal side effects. Domperidone has a better tolerability profile, even though it may occasionally associate with sedation and arterial hypotension. In the emergency department setting, intravenous ondansetron (0.3 – 0.4 mg/kg) has also been used. Antiemetics that can be used for migraine attack in paediatric age are listed in Table 2.

Table 2. Symptomatic treatment of migraine in paediatric age: Antiemetics

Medication	Route of administration	Dose
Metoclopramide	oral / iv	0.1 - 0.3 mg / kg
Domperidon	oral / rectal	0.3 - 0.6 mg / kg
Proclorperazine	oral / rectal	2.5 - 5 mg
	iv	0.15 mg / kg
Ondansetron	iv	0.3 – 0.4 mg/kg

iv = intravenous

7. INTRAVENOUS DRUGS

In the emergency department setting or in open studies, medications with known efficacy in adult age have been used in young patients with severe and prolonged migraine attacks. Dihydroergotamine (0.1-0.5 mg), in association with an oral antiemetic (metoclopramide) (0.1-0.2 mg/kg), was effective in 80% of cases in a small cohort of young patients (8-22 years) [25]. More recently, other open label studies in migrainous patients (8-17 years) focused on the efficacy of the antipsychotic prochlorperazine (0.13 mg/kg) at 1 hour from administration, with improvement in 90% of cases and pain-freedom in 50% [26]. The same drug at similar doses (0.15 mg/kg) has also been compared to ketorolac (0.5 mg/kg) in 62 migrainous patients (5-18 years), showing a higher efficacy at 1 hour with the neuroleptic (85%) compared to the NSAID (55%), with good tolerability for both drugs [27].

It should be kept in mind that in about 1/3 of young migraineurs symptomatic treatment with analgesics and NSAIDs may not be effective [28]. Therefore, in view of the encouraging results in adult age, in the last decade some trials have been conducted also in paediatric age with triptans, the most recent and specific medication for migraine [20,29,30].

8. TRIPTANS

The use of triptans has undergone rapid growth since the introduction of the first of these drugs, sumatriptan, in the symptomatic treatment if migraine in adult age. Triptans have agonist action on serotoninergic receptors 5HT1B/1D, and they have both “neurotropic” activity, characterised by inhibition of depolarization of trigeminal sensitive fibres and release of vasoactive peptides such as calcitonin-gene-related-peptide (CGRP), and “vasotropic” activity, with selective vasoconstriction of cerebral vessels. Moreover, new-generation triptans are also able to cross the blood-brain barrier and therefore they exert their action also via inhibition of the trigeminal caudal nucleus, involved in processing the dolorific information. The different molecules available have similar pharmacokinetics but different pharmacodynamics (bioavailability, time to plasmatic peak, half-life, protein binding, elimination); this explains their differences as regards clinical response and side effects. Triptans may be indicated since pubertal age; indeed, pharmacokinetics results have demonstrated similar data in adult and teenager patients, whereas data in childhood are lacking. In Italy, triptans can be prescribed from age 18 years, except sumatriptan nasal spray 10 mg that can be used in patients 12 years or older [31,32]. Triptans’ action is both on pain and on associated symptoms, especially nausea and vomiting. Adverse reactions are rare and similar for all compounds in this group, and are mostly represented by fatigue, dizziness, and xerostomia. Contraindications are hypersensitivity, ischemic vascular conditions, hepato-renal failure, poorly controlled arterial hypertension and concomitant treatment with ergot-derivatives, other medications with the same mechanism of action (5HT1B/1D agonists), or monoamino-oxidase inhibitors (MAOI). Besides, triptans’ influence on neuroendocrine system is not well known yet; preliminary data suggest that some triptans may cause an increase in β-endorphins, cortisol and GH, or an inhibition in ACTH and prolactine release. Only the triptans that have been used in studies on treatment for migraine attacks in paediatric age will be dealt with in the following paragraphs.

8.1 Sumatriptan

In a controlled trial in patients aged 8-16 years, oral sumatriptan (50-100 mg) was not superior to placebo [28]. Though, a large recent multicentre open-label study with 1-year follow-up has shown the efficacy and tolerability of the association of sumatriptan 85 mg and naproxen sodium 500 mg in the symptomatic treatment of adolescent migraineurs (12-17 years) [33]. In light of these results, "Treximet", a combined drug containing sumatriptan (10 mg) and naproxen sodium (60 mg) was approved by US Food and Drug Administration (FDA) for the treatment of migraine attacks in patients aged 12 years or older, up to a maximum dosage of sumatriptan 85 mg and naproxen sodium 500 mg. Contraindications should always be kept in mind, as well as the possible cardiovascular and gastrointestinal side effects [34].

Subcutaneous sumatriptan has also been evaluated in two open-label studies, that have demonstrated high efficacy, although this route of administration is not feasible in paediatric age [35-36]; results from controlled trials are lacking. Of higher clinical interest are data on sumatriptan nasal spray, which has shown superior to placebo in patients aged 6-17 years at doses ranging between 5 and 20 mg per attack, according to several controlled studies

[37-40]. An Italian open-label trial has also demonstrated good efficacy and tolerability of sumatriptan nasal spray in young migraineurs [41].

8.2 Zolmitriptan

Oral zolmitriptan (2.5-5 mg) may also be used in young migraineurs (12-17 years). This medication showed efficacy in an open-label study [42], although this was not confirmed in a large controlled trial [43]. A controlled study on adolescent patients has been recently conducted, confirming the superiority of zolmitriptan 2.5 mg compared to placebo, with good tolerability [44]. This same trial also compared zolmitriptan to ibuprofen (200-400 mg), with similar results for the two drugs as regards efficacy (improvement at 2 hours: 62% zolmitriptan vs 69% ibuprofen), and pain-freedom at 2 hours (45% and 48% respectively); these values were significantly superior to placebo (28% and 7%, respectively). Side effects were reported in 34% of cases with zolmitriptan, in 28% with ibuprofen and in 13% with placebo [44]. Recently, the efficacy of zolmitriptan nasal spray 5 mg in adolescent patients (12-17 years) has also been studied [45]: the efficacy at 15, 30 and 60 minutes, and pain-freedom rates at 60, 90 and 120 minutes were significantly better than placebo. Zolmitriptan's advantages are also on minor associated symptoms, on reduction in the use of symptomatic medications and on return to complete function with fewer relapses. Side effects are limited (taste disturbances) and rare (6.5%). Very recently, FDA has approved zolmitriptan nasal spray 2.5 mg in migraine with and without aura in patients ≥12 years, representing the only nasal spray authorized in patients younger than 18 years in the US. Maximum recommended dose per administration is 2.5 mg, and the total dose administered should not exceed 5 mg in 24 hours [46].

8.3 Rizatriptan

Oral rizatriptan (5 mg) did not result superior to placebo in two controlled studies [47,48], whereas in a more recent study [49] rizatriptan 5 and 10 mg resulted superior to placebo in patients 6-17 years old with good tolerability; similarly, in an open-label trial [47], rizatriptan showed high efficacy (77%). FDA has recently approved the use of rizatriptan for the treatment of acute migraine attacks in children ≥6 years (5 mg) and in adolescents ≥12 years (10 mg) [50].

8.4 Eletriptan

Eletriptan (40 mg) has also been studied, demonstrating good tolerability in patients 12-17 years old [51]. Even though it didn't result superior to placebo in a controlled trial [52], eletriptan associated to a lower relapse rate.

8.5 Almotriptan

In a large controlled trial [53], different doses of almotriptan (6.25 mg, 12.5 mg, 25 mg) were superior to placebo in relieving both the pain and some associated symptoms, such as photophobia and phonophobia, with good tolerability [54]. Another subsequent open-label study investigated tolerability further, showing efficacy and safety of almotriptan also after 1 year of treatment [55]. Oral almotriptan has recently been approved by FDA for the treatment of acute migraine attacks in adolescents ≥12 years old [56].

8.6 Frovatriptan e Naratriptan

Frovatriptan has not been studied in young migrainers yet and no trials in paediatric age are available for naratriptan either.

In summary, triptans are well tolerated in paediatric age, though their efficacy seems to be lower in children than in adults, exception made for some medications in this class with oral (rizatriptan and almotriptan) and, especially, intranasal administration (sumatriptan and zolmitriptan) [31].

The overall lower efficacy associated with the oral route of administration may be related both to the shorter duration of attacks [1], and the gastric stasis that are known to occur during migraine attacks in paediatric age [57]. As reported in some recent meta-analyses, sumatriptan nasal spray is an effective medication with a good safety and tolerability profile [20,29].

In conclusion, data on symptomatic treatment for acute migraine attacks are still scarce and limited by significant methodological limitations relative to heterogeneous classification systems and treatment protocols (dosage, route and time of administration), and small study populations. Therefore, multicentre controlled studies on symptomatic treatment of migraine conducted in large and homogeneous cohorts of paediatric patients are warranted. Cross-over methodology, rather than parallel groups, should also be undertaken, as well as enrolment of patients from

primary care centres rather than specialised centres, in order to reduce a possible selection bias.

9. PHARMACOLOGICAL PROPHYLAXIS OF MIGRAINE

This treatment option has also been the object of numerous studies in childhood [9,17,22,57-61].

The indication to undertake a prophylaxis is based on high frequency (>3/month) and intensity of attacks and/or a poor response to symptomatic treatment. The goals of preventive therapy are: a) to reduce the frequency and severity of attacks, as well as the use of symptomatic medications; b) to improve the response to symptomatic treatment; c) to reduce disability; d) to improve the function and the quality of life.

It is likely that a good therapeutic management of migraine in childhood, besides improving the quality of life, can also favourably affect the natural history of long-term illness.

On the other hand, it should be taken into account that a pharmacological prophylaxis, even if set in cycles of no more than 4-6 months, may result in a lower patient and family compliance and a in greater chance of side effects. It should not be forgotten, moreover, that migraine in children may experience periods of prolonged spontaneous remission. Therefore, before embarking on a pharmacological prophylaxis, an appropriate follow-up of at least 2-3 months is necessary to monitor the headache pattern with the aid of a clinical diary, which should also be continued during the course of treatment cycles. Also in the context of trials on pharmacological prophylaxis for migraine, the proportion of placebo-responders in children is much higher than in adults (16-55% vs. 14-34%) [16]. Generally, monotherapy should be preferred, and this should be individually tailored according to age, weight and tolerability profile (contraindications, side effects); effectiveness (headache pattern, symptomatic drugs consumption and quality of life) and side effects should be carefully monitored. After reaching clinical stability for at least 2-3 months, a gradual drug withdrawal should be planned and, in the case of inefficacy, a shift to another medication should be considered. Available data in this field are summarized in some guidelines and meta-analyses, that agree on the current limitations of controlled trials in paediatric age [3,9,59,62,17]. Indeed, data in this area there are still relatively scarce and sometimes contradictory, therefore rigorous multicentre trials should be warranted. As regards pharmacological prophylaxis of migraine in in paediatric age, 5 main drug classes are used: a) calcium channel blockers; b) anti-hypertensive drugs; c) serotonin modulators (5HT); d) antidepressants and e) antiepileptics.

Data on pharmacological prophylaxis of migraine provided by national and international guidelines [3-9] are relatively heterogeneous, exception made for topiramate and flunarizine. This last drug is nonetheless not authorised for patients under 18 years of age in some countries, like Italy, where the only drug approved for migraine prophylaxis is pizotifen from 2 years of age.

9.1 Calcium Channel Blockers

Flunarizine: Flunarizine is a drug of choice for migraine prophylaxis. In a controlled, cross-over, double-blind study in 63 subjects (age 5-11 years), flunarizine 5 mg/day produced a significant reduction in the frequency and duration of attacks compared to placebo [63]. Side effects may include increased appetite and weight gain, mild sedation, and very rarely mild extra-pyramidal symptoms (tremor), reversible after suspension of treatment. Flunarizine is registered for use from 12 year of age. The recommended dose is 5 mg/day in a single evening administration.

Cinnarizine: A recent randomised double-blind study in 44 young migraineurs (4-15 years) comparing prophylaxis with topiramate (50 mg/day) to cinnarizine (37.5-50 mg/day based on weight) for a period of 12 weeks has shown a reduction in the frequency and intensity of attacks compared to baseline in both groups, without relevant differences between the 2 treatments and with good tolerability [64].

9.2 Antihypertensive Drugs

9.2.1 Beta-blockers

β-blockers are a large class of compounds widely used in adults, and their mechanism of action in migraine prophylaxis is not yet fully understood. β-blockers dosage should be increased gradually in order to avoid side effects, which most commonly consist of bradycardia, hypotension, sweating, dry mouth, skin rash, appetite disorders, insomnia and depression.

β-blockers are contraindicated in case of bradyarrhythmias and asthma. In a very old Scandinavian controlled trial, propranolol 60-120 mg/day (1-3 mg/kg/day) was shown superior to placebo [65]; later, metoprolol (50-100 mg/day) was compared with non-pharmacological interventions (such as biofeedback and relaxation) in patients (aged 8-16 years) with different types of primary headache, reporting higher efficacy of non-pharmacological techniques, also at follow-up of 8 months [66].

9.3 Serotonin Modulators

9.3.1 Pizotifen

In a first controlled study in 37 subjects (6-15 years), pizotifen 1.5 mg/day for 3 months resulted in a significant reduction in headache frequency compared to placebo, with only modest weight gain [67]. Although, in a subsequent controlled study in 47 migraineurs (7-14 years), pizotifen 1-1.5 mg for 6 months was not superior to placebo [68]. The recommended dosage is, therefore, 1-1.5 mg/day (0.04 mg/kg/day) in a single evening administration. Side effects include sedation, increased appetite and weight gain. Contraindications are represented only by obesity.

9.3.2 Cyproheptadine

Cyproheptadine 0.2-0.4 mg/kg/day for 3-6 months was first evaluated in a pioneering open-label study, resulting in good headache improvement (68%) or remission (21%) [69]. In view of their shared antihistamine properties, side effects to cyproheptadine, which is commonly used also in younger patients, are similar to those to pizotifen, and mainly consist of drowsiness, weight gain and dizziness. Contraindications are represented by asthma, glaucoma and peptic ulcer. The recommended dosage is 0.2-0.4 mg/kg/day in a single evening administration.

9.4 Antidepressants

9.4.1 Amitriptyline

The use of amitriptyline in juvenile migraine has been evaluated only in few open-label studies. A first trial conducted in 24 subjects aged 6 to 12 years old, demonstrated a reduction in attack frequency in 75% of cases with a 2-month treatment with amitriptyline 1.5 mg/kg/day, with drop-out rates of about 20% due to side effects, mainly weight gain [70]. Two subsequent open trials are also worth mentioning: the first, conducted on 192 subjects aged 9-15 years, demonstrated efficacy of amitriptyline with variable dosage from 0.25 to 1 mg/kg/day in over 80% of cases with good tolerability [71]; these results were confirmed (89%) in a second study in 73 subjects (3-12 years), at a dosage of 10 mg/day [9]. The comparison with cyproheptadine (4 mg/twice day) and propranolol (15 mg/twice day) confirmed the superiority of amitriptyline (15 mg/day) and of ß-blockers over cyproheptadine [72]. The recommended dosage for amitriptyline is 0.25-1 mg/kg/day in divided doses. Side effects are represented by drowsiness, dry mouth, weight gain, and orthostatic hypotension. Amitriptyline is a relatively difficult drug to handle in view of its anticholinergic properties and the possible cardiotoxic effects. Amitriptyline is contraindicated in heart disease, glaucoma, and hepato-renal insufficiency.

9.4.2 Trazodone

One placebo-controlled cross-over study in 40 migraineurs (7-18 years), showed a reduction in frequency and duration of attacks with trazodone 1 mg/kg divided into three doses as well as with placebo; although, after crossing-over, a further improvement was detected only in the trazodone-treated group. Trazodone was well tolerated [73].

9.5 Antiepileptic Drugs

The use of antiepileptic drugs in childhood headaches is relatively recent [74].

9.5.1 Sodium valproate

An initial open-label study on the use of sodium valproate 15-45 mg/kg/day for 6 months in 42 subjects (7-16 years) showed an improvement of headache pattern in more than 75%, though with frequent side effects (29/42) [75]. Two years later, the efficacy of sodium valproate 500-1000 mg/day was confirmed by another open-label study in 10 patients (9-17 years) [76].

Similarly, a subsequent large multicentre study showed greater efficacy of sodium valproate to placebo, though a more frequent association with side effects (obesity, menstrual flow changes, acne) for sodium valproate [77]. The recommended dose is 15-30 mg/kg/day divided into 2-3 doses. Most common side effects are

drowsiness, weight gain, skin rash and alopecia. Sodium valproate is contraindicated in liver disease.

9.5.2 Topiramate

In 2000 the first open-label study using topiramate 1.4±0.7 mg/kg/day in 75 subjects (8-15 years of age) for a duration of 3 to 11 months showed good efficacy both on headache pattern and quality of life, measured by a disability test (PedMIDAS) [78]. Side effects were mainly cognitive (12%), and more rarely weight loss (6%) and sensory disturbances (3%). Three years later, in 24 migraineurs resistant to other prophylactic drugs, an open study with higher doses of topiramate (3.5±1.7 mg/kg/day) reported improvement both in duration (87.5%) and intensity (58.3%) of attacks, but with frequent side effects (33%), although mild [79]. Subsequently, a controlled trial in 162 subjects (6-15 years) receiving topiramate (average dose 2-3 mg/kg/day) found a reduction of average number of attacks per month compared to placebo, even though it didn't reach statistical significance (p=0.6), with substantially good tolerability [80].

Finally two other trials with topiramate in juvenile migraine prophylaxis have been published: the first, using topiramate 100 mg/day in 2 administrations, showed a significant reduction of attacks frequency, disability (PedMIDAS) and school absences [81]; the second trial, conducted in young migraineurs (12-17 years), demonstrated a significant superiority of topiramate 100 mg/day for 16 weeks compared to placebo, but not of topiramate 50 mg/day [82]. In a recent open-label study on 100 migraineurs (58 males and 42 females) with a mean age of 10.5±2.1 years, 3-month treatment with topiramate (3 mg/kg/day) led to reduction in frequency, intensity and duration of attacks, as well as the PedMIDAS score, with transient and modest side effects in 21% (body temperature rise, anorexia with weight loss, and somnolence) [83].

The recommended dosage for topiramate is therefore 1-2 mg/kg/day in 2-3 doses, with slow titration. A recent review of the literature on the use of topiramate in childhood migraine confirmed the efficacy on the frequency of attacks with a dose of 100 mg/day; this is considered the best dosage for risk/benefit ratio and good tolerability [84]. Side effects consist of appetite reduction with weight loss, paresthesias, and cognitive disorders. Contraindications consist of hypersensitivity to the components, pregnancy and lactation. Recently, the FDA approved the use of topiramate in the prophylaxis of childhood migraine.

9.5.3 Levetiracetam

In an open label study on 19 patients (3-17 years), levetiracetam 250-1500 mg/day resulted in headache remission (53%) or improvement (37%) in most of the patients, and was only rarely ineffective (10%); side effects (drowsiness and irritability) were also rare (16%) [85]. More recently an open trial of levetiracetam 20-40 mg/kg/day for 2-3 months conducted on 20 migraineurs (mean age 10.6 years) showed a significant reduction both in frequency of attacks and disability (PedMIDAS) in 18/20 patients, with rare (3/20) side effects (irritability, aggressiveness); other more serious side effects were drowsiness, irritability and/or memory deficit [86]. The use of levetiracetam in the prophylaxis of juvenile migraine, however, is still considered experimental.

9.5.4 Gabapentin

One open-label study including 18 patients (6-17 years) demonstrated good efficacy of gabapentin 15-30 mg/kg/day in 2-3 doses in 80% of cases [87]. Side effects consist of drowsiness, weight gain, skin rash and alopecia. Gabapentin is contraindicated in liver disease. No other data are available to support the use of this compound in childhood migraine.

Table 3 summarizes the most used drugs for migraine prophylaxis in children and their dosages.

Table 3. Prophylactic therapy for migraine in children: Preventive drugs

Medication	Dose	Number of daily administrations
Propranolol *	1 - 3 mg / kg	2 - 3
Flunarizine*°	5 mg	1
Pizotifen*	1 - 1.5 mg	2 - 3
Amitriptyline	0.5 - 1 mg / kg	1 - 2
Trazodone*	1 mg / kg	1 - 2
Valproate*	10 - 30 mg / kg	2 - 3
Topiramate*°	1 - 1.5 mg / kg	2 - 3

** Controlled studies °Drug > placebo*

A meta-analysis [9] on the prophylaxis of paediatric migraine concluded that only flunarizine was "likely effective". The data were however still insufficient for amitriptyline, cyproheptadine and antiepileptics (valproate, topiramate and

levetiracetam) and contradictory for propranolol and trazodone. Finally, effectiveness of clonidine, pizotifen and nimodipine was not superior to placebo. However, the results of recent studies on topiramate are encouraging [78-82].

A large randomized clinical trial on chronic migraine treatment has been published recently: 135 patients (79% females) aged 10-17 years were divided into two groups, and were treated either with cognitive behavioural therapy (CBT) combined with amitriptyline (A) (1 mg/kg/day) or with an educational approach (E) associated with amitriptyline (A) at the same dosage: at 12-month follow-up, the group treated with CBT + A showed a greater reduction both of days with headache and migraine-related disability score measured by PedMIDAS scale, compared to the group E + A. These data support efficacy of CBT in children and adolescent chronic migraine [88].

9.6 Non-pharmacological Treatment

Behavioural treatments, such as relaxation techniques, biofeedback, cognitive behavioural therapy alone or also combinations of the same [89], were used as part of the non-drug therapies for childhood migraine with positive results [90], even if mostly from open trials. These techniques are not, however, always easily accessible from the Services for the diagnosis and treatment of headaches in childhood.

10. TENSION-TYPE HEADACHE

Despite the high prevalence of tension-type headache (TTH) in children, its therapeutic management has been little investigated in paediatric age, probably in view of the limited knowledge of its pathogenetic mechanisms and the milder impact on daily activities, given the less severe intensity of the symptomatologic pattern.

The treatment of TTH is based on the resolution of the attack and the prevention of attack recurrence, using both a pharmacological and a behavioural approach, as discussed in a recent review [91].

The non-pharmacological approach remains, however, the first choice [92], while the pharmacological therapy may be indicated for the prophylaxis for more severe and recurrent cases.

10.1 Pharmacological Therapy

Differently to adult age [4], data on pharmacological treatment of TTH in children and adolescents are limited and fragmentary, and there are no definitive guidelines.

10.1.1 Symptomatic therapy

Paracetamol and NSAIDs are used with similar dosage in the acute treatment of childhood migraine and in episodic TTH. Paracetamol represents the first choice, and can also be used in younger patients [92]. Ibuprofen, while being a first-line drug for the treatment of paediatric migraine [93], has not been studied in TTH. Other NSAIDs (ketoprofen, diclofenac, naproxen), which have proven effective in the treatment of adult patients [4], have not yet been studied for the treatment of paediatric TTH.

10.1.2 Prophylactic therapy

Even in this context, controlled studies on prophylactic therapy of TTH in paediatric age are lacking and therefore the use of preventive medications is "off-label" [94]. Low-dose amitriptyline is a first option from pubertal age, though the possibility of anticholinergic side effects should be born in mind [71]. The use of magnesium in the prevention of paediatric TTH in a small open-label study gave favourable results [95].

10.2 Non Pharmacological Treatment

Behavioral therapies, such as relaxation techniques, biofeedback, cognitive behavioral therapy or associations between these treatments have been extensively investigated in TTH [89] and found effective [90,96], although for the most part in uncontrolled studies. Both biofeedback electromyographic (EMG) and thermal biofeedback [97,98] have been used, with sometimes greater efficacy than in studies conducted on adult patients [99]. Moreover a similar efficacy was observed between drug therapy and relaxation for young patients with TTH [100,101].

11. CLUSTER HEADACHE AND OTHER TACs

Regarding the drug therapy, symptomatic and preventive, cluster headaches (CH) and the other autonomic trigeminal headaches (TACs) controlled studies are lacking in developmental age, possibly due to the fact that the clinical expression is less severe (lower duration of "clusters" and longer inter-attack periods), and also due to the rarity of these forms of primary headaches in juvenile age. The therapeutic

approach to those particular forms in children is still based on data from small case series or case reports, as reported in a recent review [102].

11.1 Symptomatic Therapy

The inhalation of 100% oxygen (for 10 minutes at 7 liters/minute) was effective in paediatric age in this type of headache [103]. In the acute phase of CH, the use of steroids for 2-3 weeks should be considered [104]. Sumatriptan can be used in patients over 12 years as nasal spray (at a dose of 10 mg). The use of sumatriptan 6 mg subcutaneously is possible after the age of 14 years prior informed consent of family members. Indomethacin (25-100 mg/day orally, rectally, i.m. or i.v. in a hospital setting) may be indicated in the symptomatic treatment of patients with paroxysmal headache over 14 years [105].

11.2 Preventive Therapy

Prophylactic therapy of TACs in children should be initiated since the beginning of the crisis. In the prophylaxis of CH in children, the drug of choice is oral verapamil (20-80 mg 2-3 times/day), with proper titling and on complying with the ECG. There are also reports on the use of pizotifen (1-2 mg/day) and of flunarizine (5 mg/day) in the prophylaxis of adolescents with this rare clinical form. Finally, data on other medications (topiramate, valproate, gabapentin and lamotrigine) that are effective in adulthood are missing.

12. ALTERNATIVE THERAPIES IN PRIMARY HEADACHES

Despite the availability of several drugs for the treatment of primary headaches, there has been a growing demand for "natural" and alternative therapies whose use was the subject of a recent literature review [106].

12.1 Nutraceuticals

The term nutraceutical indicates substances that are contained in food.

12.1.1 Magnesium

The pathophysiological effects of magnesium include blockage of calcium channels and NMDA glutamate receptors and of synthesis and release of nitric oxide. Studies in children have shown low levels of intracellular magnesium [107] and, after treatment with magnesium, a significant reduction of headache attacks, of consumption of analgesics and of disability both in migraine and tension-type headache [52,95].

12.1.2 Riboflavin (vitamin B2)

This compound can increase the mitochondrial energetic efficiency, which is deficient in migraineurs. In a placebo-controlled trial [108] in 42 prepubertal subjects, 50 mg/day of riboflavin for 4 weeks, was beneficial only for the subgroup of migraine associated with tension-type headache. In two other studies in young migraineurs a greater dosage respectively to 200 mg/day [109] and 200-400 mg/day vs placebo [110] did not give satisfying results.

12.1.3 Coenzyme Q10

Coenzyme Q10 (CoQ10) is a cofactor of mitochondrial enzymes that can facilitate the production of ATP. This compound was effective in the prophylaxis of paediatric migraine in a large study [111]: About 30% of the subjects had values of CoQ10 below the reference range and supplementation of CoQ10 raised levels of this cofactor reducing both the frequency of the attacks that the degree of disability.

12.1.4 Alpha lipoic acid

Present in nature in many foods, alpha lipoic acid helps increase the mitochondrial metabolism. In a randomized placebo-controlled study, 54 subjects received 600 mg of alpha lipoic acid per day for 3 months, but no significant differences versus placebo were found [112].

12.1.5 Melatonin

In an open label study conducted for 3 months in children and adolescents (6-16 years) with migraine and chronic tension-type headache, a reduction in the frequency and duration of attacks was reported [113]. A recent open-label study evaluated the treatment with melatonin (0.3 mg/kg/day) for a period of 3 months in 60 subjects with migraine without aura (mean age: 10.3±2.4 years). The frequency, intensity and duration of the attacks was significantly reduced at the end of prophylaxis, as well as the PedMIDAS score, with side effects in 23.3% of cases, mainly consisting of daytime sleepiness and, more rarely, vomiting [114].

12.1.6 5-hydroxytryptophan (5-HTP)

Direct precursor of serotonin, 5-HTP is found in large quantities in Griffonia seeds. A controlled

study on young migraineurs showed no significant differences between the group treated with 5-HTP and the placebo group [115].

12.2 Phytotherapy

12.2.1 Petasites hybridus (butterbur)

The pharmacological effects are due to the components petasin and isopetasin, which likely have anti-inflammatory and vasoconstrictor activity. A large prospective multicenter open-label study conducted on young migraineurs found a reduction of 50% of attacks [116].

12.2.2 Tanacetum parthenium (feverfew)

The anti-migraine action is probably related to parthenolide content in the leaves. Feverfew has the properties of both inhibiting platelet aggregation and having an anti-inflammatory action. A meta-analysis did not show greater efficacy of feverfew versus placebo in adult migraine prophylaxis [117], but a subsequent multicenter study in migraineurs adults showed good efficacy [62]. Data in developmental age are lacking.

12.2.3 Ginkgo biloba

It contains ginkgolide B, capable of inhibiting the platelet-activating factor. In an open label study in patients with migraine without aura in children (8-18 years), the combination of ginkgolide B, coenzyme Q10, vitamin B2 and magnesium resulted in a significant reduction both in the frequency of headache attacks, and in analgesic consumption [118], as confirmed in another open study conducted for three months in school-age children [119]. These trials are, however, still to be validated using the single compounds.

12.3 Physical Therapy

12.3.1 Acupuncture

Many drugs used in the treatment of primary headaches in children are "off-label", and the data on their pharmacodynamic and safety profile are still lacking. In this respect, the use of acupuncture can be an option, as the efficacy results in adulthood are similar to those of drug therapies [120,121]. Pintov et al. [122] in a series of 22 young migraineurs (age 7-15 years), found an improvement in the frequency and intensity of attacks by true acupuncture, unlike the "sham" acupuncture; also the levels of endogenous opioids increased only in the group receiving true acupuncture. More recently Gottschling et al. [123] in a randomized, double-blind, placebo study compared the treatment with active laser versus placebo laser in 43 young people (average age 12.3 years) with migraine (n = 22) and tension-type headache (n = 21), according to the rules of traditional Chinese medicine. Only the active treatment was able to reduce the frequency, the intensity and the duration of headache attacks, compared both to the pre-treatment period and to the group treated with laser-placebo.

Finally, in a retrospective case study on the experience of acupuncture treatment in paediatric patients with chronic and severe pain, this procedure resulted in an improvement of pain in more than 2/3 of the treated cases [124].

A survey on the use of "alternative complementary medicine" (CAM) on a sample of 124 young subjects (aged 4-16 years) attending an Italian Specialist Centre for headaches and analyzed through a semi-structured interview has been recently published [125]. Migraineurs prevailed (82%) on patients with tension-type headache (18%). The CAM was used in 76% of the sample mainly as preventive therapy for an average period of one year. The different choices consisted of: herbal products (64%), vitamin/mineral supplements (40%), homeopathy (47%), physical therapy such as massage, shiatsu, osteopathy (45%), yoga (33%), and acupuncture (11%) [125].

In summary, this grouping of complementary and alternative therapies has not yet provided an amount of data to be inserted between the scientifically indicated principals, but it deserves more attention, especially in children, given the good tolerability profile.

13. CONCLUSIONS

Our literature review emphasized that most of the available information on paediatric primary headaches is derived from relatively low quality data, lacking randomized controlled trials and large series; therefore, results should be considered with caution, especially as regards long-term treatments such as prophylaxis.

In general there is broad agreement in considering analgesics and NSAIDs as first-line pharmacological treatments in the acute phase both for migraine and TTH in children. As

regards migraine, other medications used for attacks may include antiemetics and triptans, whereas calcium-channel blockers, antihypertensive drugs, serotonin modulators, antidepressants and antiepileptics may be used for prophylaxys. Data are more limited as regards prophylaxis of paediatric TTH, though amitriptyline and magnesium have been used in these cases. Non pharmacological interventions may also provide useful in both headache types, as well as alternative therapies, also in view of their more favourable tolerability profile. The high placebo response and incomplete knowledge on the pharmacodynamics of the various products in children exacerbate medico-legal issues related to the often use "off-label" of many compounds, especially in the field of prophylaxis. The present state of knowledge and given the limitations in the use of certain medications in children (eg. possibility to use some NSAIDs only after the age of 12 years, and oral triptans only after age 18), a "layered" approach, which involves the use of a particular type of drug on the basis of the type of the attack in the individual patient, is therefore not feasible especially in young migraineurs. Therefore a "gradual" approach remains possible, which is based on the choice of drugs in stages, from the more manageable ones to the most effective ones. The treatment of headaches in children remains, therefore, a still little explored field and the various treatment options should be based not only on the characteristics of the attacks and the clinical form, but especially on those of the individual patient on which to tailor specific treatment [21,126]. The latter must take into account different aspects (biological, psychological, social and family) that are intertwined in determining the condition of the headache sufferer. An accurate diagnostic approach, early and adequate treatment of the young migraineur, other than reducing disability and improving the quality of life, can help modify the natural history of a disorder that otherwise tends to persist into adulthood in about 50% of the cases, and may sometimes become chronic, exposing to the risk of drug abuse. Comprehensive meta-analyses [9,14,59] should provide a base for future trials, to be conducted with the most appropriate methods. New controlled and more rigorous trials, especially in the field of migraine prophylaxis in children, should be undertaken. Such trials can now make use of the best standardized criteria for diagnosis (51), and for assessing the effectiveness, tolerability and safety of the drugs used [127].

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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