

Pediatric Migraine Treatment: An Updated Review

Marcello Pasculli^{1*}, Pasquale Striano² and Maria Giuseppina Ledda³

¹Child and Adolescent Neuropsychiatric Unit, Department of Biomedical Science, University of Cagliari, "A. Cao" Microcitemico Pediatric Hospital - G. Brotzu Hospital Trust, Cagliari, Italy

²Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, "G. Gaslini" Institute, Genova, Italy

³"A. Cao" Microcitemico Pediatric Hospital - G. Brotzu Hospital Trust, Cagliari, Italy

*Corresponding author: Marcello Pasculli, Child and Adolescent Neuropsychiatric Unit, Department of Biomedical Science, University of Cagliari, "A. Cao" Microcitemico Pediatric Hospital - G. Brotzu Hospital Trust, Cagliari, Italy, Tel: +393271797162; E-mail: marcellopasculli@tiscali.it

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Abstract

Introduction: Migraine is the most important cause of pediatric consultations due to headaches, because of significant distress and disability for child and their family. For this reason, a correct and timely treatment is very important.

Objectives and methodology: This article reviews the current knowledge about migraine treatments in children and adolescents. With the term "migraine" we refer to all migraine subtypes. Literature search was carried out in PubMed for all studies and reviews published until December 31st, 2018.

Results: The treatment of pediatric migraine is multidisciplinary. It is based on an integrated biobehavioral approach and a pharmacological intervention with use of symptomatic and/or prophylactic drugs.

Discussion: In the literature, data on the current clinical practice on treatment of pediatric migraine are very limited. We evaluated the use of acute and preventive drugs, nutraceuticals and non-pharmacological treatments.

Acute or symptomatic treatment is always more effective when given early during the attack. NSAIDs, especially ibuprofen, should be preferred to acetaminophen for treating acute attacks of migraine, because they were usually more effective and well tolerated. If NSAID are not effective, triptans could be used more frequently as first for treating migraine attack in adolescents.

Migraine prophylaxis includes a large number of drugs but relatively few rigorous, randomized controlled studies have been carried out in children and adolescents. According to the main guidelines or systematic reviews for preventive treatment of paediatric migraine flunarizine is recognized as the first choice drug for prophylaxis, followed by propranolol, amitriptyline, pizotifen, cyproheptadine and antiepileptic drugs (topiramate and valproate).

Therefore, the use of *non-pharmacological treatments* should be implemented in clinical practice, especially in cases with contraindications or poor tolerability or efficacy to preventive drugs.

Conclusions: Pediatric RCTs, based on larger samples sizes and innovative study protocols, involving multicenter studies and primary care services (to reduce selection bias), are needed to better understand the most effective and safe treatment strategies for pediatric migraine patients and define "responders" profile.

Keywords: Migraine; Treatment; Children; Adolescents; Pharmacological and non-pharmacological treatment migraine and children; Pediatric treatment; Drugs for acute and chronic migraine treatment in children

Introduction

Migraine is the most important cause of pediatric consultations due to headaches [1-3] because of significant distress and disability for child and their family [4]. For this reason, a correct and timely treatment is very important.

Epidemiology

More than half of migraineurs have their attack before they're 15 years of age [5]. The mean age of onset of migraine is 7 years in boys and 11 years in girls [6]. The overall mean prevalence of migraine in the pediatric population is 9.1% (95% CI 7.1-11.1) [1]. According an extensive review of 64 cross-sectional studies, published in 32 different countries, including a total of 227,249 subjects, the prevalence of migraine steadily increases through childhood. The male:female ratio shifts during adolescence according to the age (increases with age) and the gender [7] (Table 1).

By ages	Preschool	Elementary school	High school
Prevalence (%)	1.2-3.2	4-11	8-23
Gender ratio	boys>girls	boys=girls	girls>boys

Table 1: Prevalence of migraine headache through childhood [1].

Classification

Formal diagnostic criteria for primary and secondary headaches have been revised and published in the International Classification of Headache Disorders, 3rd edition. Headache Classification Committee of the International Headache Society (IHS) classified migraine into different subtypes: a) migraine without aura, b) migraine with aura, c) chronic migraine, d) complications of migraine, e) probable migraine, and f) multiple episodic syndromes that may be associated with migraine [8].

Diagnostic evaluation

The diagnosis is based on clinical criteria established by the International Classification of Headache Disorders, 3rd edition (ICHD-3) [7]. Detailed clinical history and general neurologic examination [9,10] are very important to distinguish between primary and secondary headache and to make the correct diagnosis and to choose the appropriate therapies (Tables 2 and 3).

Cause	Result
Elevated ICP	Hydrocephalus, idiopathic intracranial hypertension, medications, exogenous hormones, tumor, vascular malformation, large cyst, cerebral edema
Low ICP	CSF leak, consider with trauma or connective tissue disorder
Infection	Viral illness, systemic infection, sinusitis, strep pharyngitis, meningitis/encephalitis, fungal meningitis may be indolent
Cerebrovascular disease	Hemorrhage, vascular dissection, venous thrombosis, ischemic stroke, vascular malformation, vasculitis
Trauma	Posttraumatic headache, intracranial hemorrhage, whiplash/cervicogenic headache, vascular dissection
Medications	Antihypertensives, amphetamines, stimulants, nitrates, some antibiotics, IVIG, steroids, exogenous hormones, vitamin A, retinoic acid, caffeine, opioids, cannabis, NSAIDs, metronidazole
Metabolic disease	Endocrine disorder, hypercapnia/sleep apnea, mitochondrial disease, eating disorder/fasting, celiac disease
Toxic exposure	Alcohol, drugs, inhalants, lead
Epilepsy	Post- or preictal headaches
Rheumatological disease	Aseptic meningitis, intracranial hypertension, cerebrovascular disease, immunosuppressive agents, and NSAIDs
Dental disease	TMJ, dental caries, abscesses

Table 2: Potential causes of secondary headache [4].

Family history of migraine
Childhood migraine proxy symptoms: carsickness, gastrointestinal complaints
Age of onset
Frequency, severity and changes over time
Triggering, aggravating or alleviating features
Autonomic features
Aura features
Current and prior treatments
Lifestyle features
Comorbid conditions

Table 3: Essential elements of the headache history [11].

It is not supported by laboratory or other specific examinations. Neuroimaging should be considered when various “red flags”, warning symptoms and signs suggestive of a secondary headache, are present (Table 4) [12]. Electroencephalography (EEG) is recommended only in case of an underlying seizure disorder [13]. Lumbar puncture, in the same way, should be performed only in a suspicion of subarachnoid hemorrhage or neurological infections.

New headache type or progressive increase in severity and frequency of headache
Sudden onset of severe headache (<6 months in duration)
Changing of quality of headache (exacerbation of headache with straining, sneezing or coughing)
Symptoms of systemic disease which may include weight loss, night sweats, fever, joint pains, rash, stiff neck...
Known systemic disorder, including neurocutaneous syndrome, hypercoagulopathy, genetic disorder, malignancy with possible metastases, rheumatological disorder, immunosuppression
Abnormal neurological examination, including focal neurologic or symptoms (other than typical aura), ataxia, cranial nerve deficit, head-tilt, papilledema, visual impairment, altered mental status (decreased consciousness level) or other abnormalities
Young age of child (<6 years old)
Headaches suggesting raised intracranial pressure (early morning headache, vomiting in morning, pain disturbing sleep, headache worse cough or valsava)
Signs of head trauma
Ventriculoperitoneal shunt

Table 4: Red flags for secondary headache [4,5].

Objectives and Methodology

This article reviews the current knowledge about treatment of migraine in children and adolescents. With the term “migraine” we refers to all the above indicates subtypes.

Literature search was carried out in PubMed for all studies and reviews published until August 31st, 2018. The keywords searched for were “treatment migraine and children”, “pharmacological and non-pharmacological treatment migraine and children”, “prophylactic/preventive treatment migraine and children” and “drugs for the acute treatment of migraine in children”. Studies were included if they focused on the pediatric population, if they were published in peer reviewed journals and written in English.

Results

The treatment of pediatric migraine is multidisciplinary and includes pharmacological and non-pharmacological interventions [14].

Approximately 60% of children and adolescents with migraine will improve with a three-pronged treatment approach that includes general measures, acute and preventive pharmacological and non-pharmacological treatments [15]. Therapeutic strategies should be

based not only on the characteristics of the migraine episodes, the daily migraine disability and the impact on quality of life [8], measured by PedMIDAS and PedsQL 4.0 Course Scale [16,17], but especially on the biological (patient’s age), socio-family (family structure, culture, beliefs) and psychological aspects of patients [17,18].

For the remaining 40% of children and adolescents having continuous headache or medication-overuse headache, the clinician’s judgment remains the best guide to preventive therapy selection.

General Measures

Lifestyle modifications

The first step in avoiding migraine attack is to recognize and to eliminate triggering factors such as: poor sleep habits, dietary (irregular meals, alcoholic beverages, caffeine excess, nitrates and nitrites, foods with tyramine), environmental (media abuse, odors), medication (estrogen, histamine, nifedipine, ranitidine, reserpine...), psychological (stress, anxiety, worry, depression) and physical triggers (fever, fatigue, hypoglycemia, dehydration) [10]. Any trigger factors should be addressed and modified when possible, to promote general health (SMART, Sleep, Meals, Activity, Relaxation Trigger avoidance) (Table 5) [19].

Sleep	Regular and sufficient sleep
Meals	Regular and sufficient meals, including breakfast and good hydration
Activity	Regular (but not excessive) aerobic exercise
Relaxation	Relaxation, stress reduction and management
Trigger avoidance	Avoid triggers such as stress, sleep deprivation or other identified triggers

Table 5: SMART: Lifestyle changes to promote general health [19].

Acute Treatment

Acute treatment includes abortive (or rescue) medications that are taken during acute migraine attack to provide quick relief from headache.

Drug used in symptomatic treatment are chosen according to the headache type and frequency, type of symptoms associated, their adverse-effect profile and comorbidities.

The common goals of acute treatment are: reduction or removal of pain and associated symptoms, recover of the global functioning, reduction or removal of side effects, improvement of the quality of life and reduction or removal headache recurrences. Their use should be limited to no more than two to three times per week to avoid Medication Overuse Headache (MOH).

The main indications are: migraine attacks with limited frequency (≤ 4 episodes/month), contraindications to prophylaxis therapies and poor compliance to prophylaxis therapy.

Lastly we remind you that in pediatric age the share of placebo-responders to symptomatic migraine therapy is even higher (40-70%) than the adult (30-45%), so that the results in the controlled trials are less comprehensible and more difficult [8].

Analgesics and NSAIDs

Paracetamol (or acetaminophen) and ibuprofen are the most commonly used over-the counter (OTC) drugs. Few and limited controlled studies have been performed on the use of analgesics in the pediatric migraine.

Regarding acetaminophen, there isn’t sufficient evidence for the acute treatment of migraine in children and adolescents. In a double-blind, randomized, placebo-controlled, crossover study acetaminophen (15 mg/kg) was not superior to placebo or ibuprofen (7.5-10 mg/kg), while ibuprofen was significantly more effective than placebo and in reducing pain intensity [9,13,20,21].

The rare adverse effects of acetaminophen are skin rash, erythema, urticaria, while gastralgia, nausea and vomiting for ibuprofen. At the moment, acetaminophen is not contraindicated as an analgesic since the first years of life. Contraindications are drug hypersensitivity, liver failure and haemolytic anemia [22].

Ibuprofen is another NSAID (Non-Steroidal anti-Inflammatory Drug) used in the acute treatment of migraine in children [23]. Treatment should be initiated at the onset of pain or aura, if present, even before the head pain begins. The initial dose could be repeated once in 4-6 h for the same headache, if needed.

Ketorolac is used mostly in the emergency department. It is used an intravenous formula, starting from 0.5 mg/kg. It is effective in 55.2% of the patients in one hour. When combined with prochlorperazine, the response rate improves to 93% [24]. According a randomized, double-blind trial of prochlorperazine versus ketorolac, recurrence rate within 24 h with ketorolac alone is 30% [25].

Indomethacin is another NSAID used in a heterogeneous group of headache such as Valsalva-induced headaches (cough, exercise or sex headache), primary stabbing headache, hypnic headache and the trigeminal autonomic cephalalgias (TACs) [a group of primary headache disorders that includes cluster headache (CH), paroxysmal hemicrania (PH), hemicrania continua (HC) and short-lasting

unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA)] [26].

Its mechanisms are not clear. It is a reversible inhibitor of prostaglandins, blocking both COX-1 and COX-2 synthesis.

Treatment usually starts with a dose of 25 mg three times daily with meals, and a response is usually fast. Otherwise after 48 hours the dosage can be increased to 50 mg three times daily. The most important side effects are vomiting, upset stomach, heartburn, diarrhea, a feeling of bowel fullness, constipation, bloating, gas, rectal irritation, dizziness, drowsiness, nervousness, headache, skin rash, itching or blurred vision.

Drug (type of drug)	Dose (maximum/dose)	Adverse effects	Contraindication/cautions
Paracetamol or acetaminophen*	15 mg/kg/dose PO (1000 mg) or PR q 4 h	Skin rash, erythema, urticaria	Drug hypersensitivity, liver failure, severe hemolytic anemia
Ibuprofen* (NSAID)	10 mg/kg/dose PO, q 6 h (800 mg)	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	Liver failure, glucose 6 phosphate dehydrogenase deficiency, hemorrhagic diseases, <6 months
Ketoprofen (NSAID)	1-2 mg/kg PO	Ulcers and gastric bleeding, constipation, diarrhea, sores in the mouth, dizziness, nervousness, drowsiness, insomnia, tinnitus,	Drug hypersensitivity, asthma, <6 years
Ketorolac (NSAID)	30 mg initial dose, then 15-30 mg/dose (0.5 mg/kg) IV or IM 10 mg/dose PO, q 4-6 h	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	Gastro pain, nasty taste, flushing, confusion <16 years; renal impairment
Diclofenac (NSAID)	0.5-1 mg/kg PO (150 mg) 0.5-1 mg/kg IV/IM (150 mg)	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	Gastro pain, bleeding, ulceration, allergic reactions, <6 years
Piroxicam (NSAID)	10-20 mg/kg	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	<6 years
Naproxen sodium (NSAID)	5-7 mg/kg PO (500 mg)	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	<16 years
Acetylsalicylic acid (NSAID)	10-15 mg/kg/dose PO up to 6 doses/day	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	<16 years
Nimesulide (NSAID)	1-2 mg/kg PO (400 mg)	Gastralgia, gastric burning, nausea, vomiting, rarely gastric and duodenal ulcer, rash and urticarial reactions, asthmatic crises, anaphylaxis	>18 years

IM: Intramuscular; IV: intravenous; NSAIDs: Nonsteroidal Anti-inflammatory Drug ; PO: by months; q: every
*Controlled studies.

Table 6: Analgesics and NSAIDs [12].

Alternative over-the-counter anti-inflammatory medications, including naproxen sodium and aspirin. Naproxen is a different NSAID that, when given in combination with sumatriptan, is FDA approved for use in pediatric migraineurs. Aspirin should be avoided

in children under the age of 16 years to avoid the risk of Reye syndrome [13].

In the current body of literature, there is no evidence for use of diclofenac in children with migraine.

Table 6 summarizes the most common analgesics and NSAIDs, their doses, adverse effects and contraindications.

Antidopaminergic agents

Antidopaminergic agents, such as prochlorperazine and metoclopramide, are indicated in the treatment of significant nausea and vomiting associated with migraine attack, in the emergency department (ED). A multi-center retrospective study of common practices in the ED for management of migraine compared numerous treatments (non-opioid analgesics, dopamine agonists and diphenhydramine): prochlorperazine was used with equal frequency to metoclopramide and appeared more effective than metoclopramide in preventing the return of patients in the ED [27]. In a 2011 study has been showed that prochlorperazine, when given intravenously with a load of intravenous fluids, determined a 75% improvement with 50% headache freedom at 1 h, and 95% improvement with 60% headache

freedom at 3 h [13,28]. However, given the risk of dystonic reaction, it is usually recommended the combination with diphenhydramine. Its sedating effect could be beneficial for patients who need to sleep after their migraine attack [4]. One randomized double-blinded study comparing prochlorperazine and intravenous ketorolac found that prochlorperazine was more effective than ketorolac in reducing recurrence rate within 24 h [29].

Other neuroleptics, administered via the parental route, for the management of status migrainosus include haloperidol and chlorpromazine. Only one pediatric retrospective study of the IV use of chlorpromazine versus prochlorperazine found higher rate of relapse and side effects in the chlorpromazine group.

At the moment, there have not been carried out prospective study about the efficacy of intravenous neuroleptics in migraineurs children (Table 7) [30,31].

Drug (type of drug)	Dose (maximum/dose)	Adverse effects	Contraindications
Prochlorperazine	PO/PR: 2.5-5 mg/kg IM: 6.25 mg, max three time/die IV: 0.15 mg/kg (10 mg)	Sedation, dystonia, akathisia, tardive dyskinesia, all rare	<2 years; long QT syndrome, movement disorder
Chlorpromazine	1 mg/kg/die PO	Dystonia, akathisia, tardive dyskinesia, all rare	
Metoclopramide	0.1-0.3 mg/kg PO/IV (10 mg)	Dystonia, akathisia, tardive dyskinesia, all rare	Long QT syndrome, movement disorder

IM: Intramuscular; IV: intravenous; NSAIDs: Nonsteroidal Anti-inflammatory Drug ; PO: by mouth; PR: Per Rectum

Table 7: Antidopaminergic agents [12].

Ergot-based therapies

The use of ergot alkaloids should be limited for their vasoconstrictive properties. The effect of dihydroergotamine is due to its 5HT-1A-1B-1D-1F receptor agonist affinity leading to central vasoconstriction. Common side effects include nausea, vomiting, abdominal discomfort, flushed face, muscle cramps, vasospasm, transient elevations in blood pressure and bradycardia [32].

Oral dihydroergotamine is not effective in the acute treatment of migraine in children and adolescents. In a small cross-over study dihydroergotamine was not more effective to placebo [33].

Triptans

Triptans are 5-HT_{1B/1D} serotonergic receptors agonists and have an anti-migraine and antiemetic action. Triptans cause the cephalic vessels vasoconstriction, inhibiting the trigeminal perivascular nerve terminals and the release of vasoactive neuropeptides [34,35]. There are different formulations of triptans as injections (sumatriptan), nasal spray (sumatriptan and zolmitriptan), tablets (sumatriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, naratriptan and frovatriptan) and dissolving tablets (zolmitriptan and rizatriptan). The intranasal, sublingual or subcutaneous route may be preferable in patients who have migraine associated with significant nausea and vomiting. Furthermore, the intranasal route may be preferable in patients who are unable to swallow pills [36]. Commonly adverse

events include fatigue, dizziness, dry mouth, and nausea or vomiting with oral preparations, and taste disturbance, nasal symptoms, and nausea with intranasal preparations. If this happens, it is worth trying a different triptan or formulation.

According the most recent practice parameter guidelines for treatment of pediatric headaches analgesics and triptans are recommended as the first-line treatment for acute migraine [37]. Triptans are used to treat moderate or severe migraine attacks, while analgesics are reserved for mild or moderate ones. The triptan should be taken at the onset of migraine and may be repeated after two hours if required. It is necessary to give the patient and parent clear instructions on the maximum dose, “two doses in 24 hours and on no more than two days a week” to prevent transformation into an analgesic overuse headache (AOH). Contraindications are hypersensitivity to triptans, cerebrovascular or peripheral vascular syndromes, severe hepatic impairment, uncontrolled hypertension, hemiplegic migraine, pregnancy, and combinations with monoamine-oxidase inhibitors, ergot alkaloids or other 5-HT_{1B/1D} agonists (increasing the risk of serotonin syndrome).

Triptans should be considered as an acute treatment option for children and adolescents with migraines, although their use is mostly ‘off-label’ (Table 8). Few triptans have been approved by the US Food and Drug Administration (FDA) for children migraine abortive therapy. In Italy only intranasal sumatriptan 10 mg is authorized from 12 years [38].

Drug	Age	Dose	Adverse effects	Contraindication
Sumatriptan	6-9 years*	PO: 25 mg at onset, repeat once after at least 2 hours if needed, max 2 days/week	Chest pain, flushing, tingling, tightness, flushing, dizziness, nasty taste (nasal spray)	<6 years
AIFA and FDA >18 years	10-17 years*	PO: 50-100 mg at onset, repeat once after at least 2 hours if needed, max 2 days/week		-
AIFA and FDA >12 years		IN: 10 mg at onset, repeat once after at least 2 hours if needed, max 40 mg/day, max 2 days/week		<12 years
AIFA and FDA >18 years		IN: 20 mg at onset, repeat once after at least 2 hours if needed, max 2 days/week SQ: 6 mg at onset, repeat once after at least 1 hour, max 2 days/week		<18 years; pregnancy; history of stroke, TIA, peripheral vascular disease, WPW syndrome
Rizatriptan FDA approved >6 years;		PO: 5-10 mg	Chest pain, flushing, tingling, tightness, flushing, dizziness, nasty taste (nasal spray)	<6 years; pregnancy
Zolmitriptan FDA approved >12 years		PO: 2.5-5 mg IN: 5 mg at onset, repeat once after at least 2 hours, max 10 mg/day, max 2 days/week	Chest pain, flushing, tingling, tightness, flushing, dizziness, nasty taste (nasal spray)	<12 years; pregnancy
Almotriptan FDA approved >12 years		PO: 6.25-12.5 mg		<12 years

FDA: US Food and Drug Administration; AIFA: Italian Medicines Agency; IM: Intramuscular; IN: intranasal; IV: intravenous; NSAIDs: Nonsteroidal Anti-inflammatory Drug ; PO: by months; SQ: subcutaneous
*FDA: "off label" in younger children

Table 8: Triptans [12].

According to a recent review on acute pharmacological treatment of migraine in children and adolescents, including 27 clinical studies, triptans appear to be effective in treating of pediatric migraine [21] (Tables 9 and 10). Generally triptans are safe, however show an increased risk of minor adverse events. No statistically significant differences regarding efficacy were found between the different subgroups of triptans: rizatriptan, sumatriptan and zolmitriptan were statistically more effective than placebo. It must be remembered that

interpretation of results among studies of triptan efficacy in adolescents is difficult for the presence of high placebo response rates [39]. No statistically significant difference regarding efficacy was found between oral and intranasal triptans. Patients may prefer oral preparations in case of chronic rhinitis or intranasal preparations if they vomit. The association with non-steroidal anti-inflammatory drugs (NSAIDs) increases triptan's effectiveness.

Study or Subgroup	Triptan n/N	Placebo n/N	Risk Ratio
1. Rizatriptan			
Ho 2012	39/98	31/102	1.31[0.89, 1.92]
Subtotal (95%, CI) Total events	98	102	1.31[0.89, 1.92]
2. Sumatriptan			
Ueberall 1999	9/14	2/14	4.50 [1.18, 17.21]
Hamalen 2002	27/59	15/58	
Subtotal (95%, CI) Total events	73	72	1.77 [1.06, 2.97]

Total (95% CI)	171	174	1.67 [1.00, 5.23]
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Table 9: Comparison between triptans versus placebo in children, outcome Pain free [40].

Study or Subgroup	Triptan		Placebo		Risk Ratio
	Events	Total	Events	Total	
1. Almotriptan					
Linder 2008	212	544	50	170	1.10[0.88, 1.39]
Subtotal (95%, CI) Total events	212	544	50	170	1.10 [0.88, 1.39]
2. Eletriptan					
Winner 2007	31	141	20	133	1.46 [0.88, 2.43]
Subtotal (95%, CI) Total events	31	141	20	133	1.46 [0.88, 2.43]
3. Naratriptan					
Rothner 1997	52	226	16	74	1.06 [0.65, 1.75]
Subtotal (95%, CI) Total events	52	226	16	74	1.06 [0.65, 1.75]
4. Rizatriptan					
Winner 2002	48	149	40	142	1.14 [0.81, 1.62]
Visser 2004	91	233	75	240	1.25 [0.98, 1.60]
Ahonen 2006	34	96	17	96	2.00 [1.20, 3.33]
Ho 20012	87	284	52	286	1.41 [1.07, 1.87]
Subtotal (95%, CI) Total events	260	762	194	764	1.34 [1.13, 1.60]
5. Sumatriptan					
Hamalainen 1997	5	23	2	23	2.5 [0.54, 11.8]
Winner 1997	59	222	14	76	1.42 [0.94, 2.39]
Rothner 1999a	43	208	10	35	1.20 [0.45, 3.18]
Rothner 1999b	9	62	3	30	1.45 [0.42, 4.98]
Rothner 1999c	11	66	5	36	1.20 [0.45, 3.18]
Winner 2000	116	377	32	130	1.25 [0.89, 1.75]
Ahonen 2004	26	83	17	83	1.53 [0.90, 2.6]
Winner 2005	191	483	68	242	1.41 [1.12, 1.77]
Callenbach 2007	12	46	9	46	1.33 [0.62, 2.86]
Fujita 2014	16	74	20	70	0.76 [0.43, 1.34]
Subtotal (95%, CI) Total events	487	1644	180	771	1.27 [1.10, 1.48]
6. Zolmitriptan					

Ewers 2005	6	14	1	14	6.00 [0.83, 43.59]
Rothner 2005	108	483	32	162	1.13 [0.80, 1.51]
Lewis 2007	58	148	24	127	2.07 [1.37, 3.13]
Subtotal (95% CI)	259	933	50	599	1.66 [1.16, 2.38]
Total events					
Total (95% CI)	1300	4250	577	2511	1.32 [1.19, 1.47]

Table 10: Comparison between triptans versus placebo in adolescents, outcome pain free [40].

Sumatriptan remains the most widely studied of the triptans. This, in combination with naproxen sodium, is more effective than placebo in treating adolescent migraine attack (in producing pain freedom), while there aren't studies in children [22].

Intranasal sumatriptan is safe and effective in children moderate or severe migraine attack: in a randomized, double blind, placebo-controlled study a statistical difference, in producing pain freedom, was found at 2 hours in those who took the 20 mg nasal spray dose than placebo group [36,41]. The main side effect is taste disturbance.

An open-label study on the subcutaneous sumatriptan in treating of children and adolescents with migraine in the emergency department showed an overall efficacy of 72% at 30 min and 78% at 2 h, with a recurrence rate of 6% [42].

There are conflicting evidences regarding other triptans. Different American studies showed that oral and nasal spray Zolmitriptan is well tolerated and effective in improving headache symptoms [43,44].

Rizatriptan has been approved by FDA for the treatment of acute migraine after 6 years, using 5 mg for children less than 39 kg and 10 mg for those 40 kg or more. A randomized, placebo-controlled trial showed that rizatriptan has been well tolerated with minimal adverse effects including dizziness, somnolence, dry mouth [45,46].

FDA approved Almotriptan for the treatment of acute migraine after 12 years. It is more effective in the treatment of migraine attack than placebo, at the 12.5 mg dose [47].

No significant statistically difference has been showed between Eletriptan and placebo in improving pain at 2 hours post-dose [48].

Magnesium sulfate

Intravenous magnesium sulfate is increasingly being used in ED acutely for the treatment of pediatric headache; however there is a paucity of evidence for its use in children with headache.

A pediatric case series reported that patients with migraine ages 5 to 18 years old treated with a standard dose of intravenous magnesium sulfate (30 mg/kg of IV magnesium sulfate with maximum dose of 2000 mg) showed a favorable response in 35% of children and experienced minimal side-effects [49].

Preventive Treatment

The main indications of preventive treatment are high frequency of migraine attacks (1 to 2 per week or >3 to 4 per month), impairment of both the quality of life (e.g., lower score on PedsQL) and the daily activities (e.g., PedMIDAS score greater than 30 or Grade III or Grade

IV), severe and prolonged attacks (>4 h), irregularity of school attendance and the ineffective, not tolerated, contraindicated or overused acute treatment of migraine attacks. In addition, we remember the presence of complex and severe accompanying symptoms or long uncomfortable aura symptoms [50-52]. The choice of the preventive drug should take into account any comorbidity, such as anxiety and depression. Although 1/3 of adolescent migraine patients have the criteria to undertake pharmacological prophylaxis, this is proposed in less than 20% of these patients [53].

Pain improvement is a gradual process and will not be instantaneous. For this reason, any drug used for prophylactic treatment should be evaluated for about 6-12 weeks before it can be considered ineffective. If effective, the medication should be continued for 6 months [54,55].

Prophylaxis treatment can be interrupted when severe migraine attacks are reduced to one or two per month (for 3-6 months). This period may be altered based on the school year. Children typically have improved headaches over the summer when they are out of school, so early summer provides an opportunity to reduce medication. Headaches often worsen with the start of school, in late spring and fall; thus, these are less desirable times to discontinue preventive medication [56].

The most commonly used medications for migraine prophylaxis are: beta blockers (propranolol), calcium channel blockers (flunarizine), the antihistaminics drugs (cyproheptadine), the antidepressants (amitriptyline) and the anticonvulsivants (valproate, topiramate and gabapentin) (Table 11).

β-Blockers

Beta-blockers, particularly propranolol, are considered first-line prophylactic drugs in the majority of the available guidelines and systematic reviews. In the Italian guidelines [57] propranolol is listed as a second choice prophylaxis drug for pediatric migraine and some systematic review [58] report conflicting evidence about its use. Their action mechanism in migraine prophylaxis is not completely understood.

Propranolol: Propranolol is a nonselective beta-adrenergic receptor blocker [59]. In older studies have been observed conflicting results. In a prospective, double-blind trial found a significant reduction of headache frequency with propranolol compared with placebo [60], while in another prospective, double blind crossover trial did not find any significant difference [61]. Recent comparative studies showed the effectiveness of propranolol in reducing headache frequency in children with migraine. In two randomized, prospective studies, comparing propranolol and sodium valproate, have been showed a significant

reduction in headache frequency, but did not found a significant statistically difference between propranolol and valproate [61,62]. Equal efficacy in reducing of headache frequency has been found in an open, randomized comparison of propranolol and cinnarizine [63]. Propranolol efficacy in reducing the frequency and duration of pediatric migraine headache has been compared with pregabalin: a significant difference between these two groups was found [64].

All these studies have suggested the efficacy of propranolol in pediatric migraine treatment but results have been limited because none of the studies used placebo controls.

Usually the starting dose is 1 mg/kg divided in three doses without exceeding 4 mg/kg per day. Adverse effects are hypotension, dizziness and depression. Contraindications include asthma, diabetes, orthostatic hypotension and depression.

Medication	Dosage mg/kg per day (maximum/dose)	Recommended daily dose	Adverse effects	Recommendation level
Amitriptyline	0.5-1 mg/kg (10 mg)	10-75 mg qhs	Dry mouth, dry eyes, lightheadedness, dizziness, constipation, increased appetite, somnolence, prolonged QT	Class IV
Nortriptyline	10 mg	10-75 mg qhs	Cardiac (arrhythmia)	No data
Topiramate	0.5-1 mg/kg/day	1-10 mg/kg/day	Numbness, weight loss, cognitive impairment, fatigue, nausea, somnolence	Class IV
Valproic acid	15-40 mg/kg/day	250 -1000 mg/day	Somnolence, skin rash, weight gain, tremor, drowsiness, hair loss, hematological or liver abnormalities	Class IV
Zonisamide	1-2 mg/kg/day	100-600 mg/day	Dizziness, nausea, irritability, somnolence	Class IV
Gabapentin	10-40 mg/kg/day	300-1200 mg tid	Sedation, ataxia, fatigue, peripheral edema	Class IV
Levetiracetam	250 mg/day	500-1500 mg bid	Dizziness, fatigue, irritability, somnolence	Class IV
Cyproheptadine	0.2 mg/kg/day	0.25-1.5 mg/kg/day	Sleepiness, weight gain, increased appetite	Class IV
Propranolol	1-3 mg	2-4 mg/kg/day	Hypotension, depression, dizziness	Class II
Flunarizine	0.1-0.3 mg/kg/day (10 mg)	5-10 mg qhs	Sedation, weight gain, fatigue, gastrointestinal discomfort	Class I
Botulinum toxin	155 units	100 units	Redness, temporary pain at the injection site, ptosis, blurred vision	Class IV

qhs: every night before bedtimes; bid: twice daily; tid: three times daily

Table 11: Preventive treatments [65].

Calcium channel blockers

Flunarizine: Flunarizine is a nonselective calcium ion entry blocker. It acts on T-type ion channels [66]. Its actions in migraine prevention are still unknown.

In two double-blind, placebo-controlled trials, children treated with flunarizine showed a significant reduction in headache frequency [67,68]. In a retrospective observational study, evaluating the flunarizine effects in different subtypes of migraine, was found a greater efficacy of flunarizine in the hemiplegic migraine [68]. A recent retrospective study comparing flunarizine and topiramate in pediatric migraine prevention showed similar effectiveness between the two drugs [69].

The recommended daily dose is 5-10 mg (every night at bedtime). The most common advent effects are sedation, weigh gain, fatigue and gastrointestinal discomfort [70].

According to the main guidelines or systematic reviews for preventive treatment of paediatric migraine flunarizine is recognized as the first choice drug for prophylaxis [55,71,72].

Antagonists of serotonin

Cyproheptadine: It is an antihistamine drug with anti-serotonergic, anti-cholinergic and calcium-blocking properties.

It is used for the prevention of pediatric migraine since the 1970s. No good scientific evidence supports the use of cyproheptadine in the pediatric population, but many clinicians use these medications with

success over decades. A recent retrospective study and an open label study in children migraineurs under 12 years, treated with cyproheptadine at doses of 0.2-0.4 mg/kg/day, showed its effectiveness in reducing headache frequency. The combination of propranolol and cyproheptadine is most effective [73,74].

It is available in a liquid form for younger migraineurs who cannot swallow pills.

The daily dose varies from 2 to 8 mg/kg and may be administered in a single dose at bedtime, in order to avoid daytime sleepiness. Adverse effects include increased appetite, weight gain and somnolence.

Pizotifen: It is a serotoninergic antagonist that acts primarily on 5-HT_{2A} and 5HT_{2C} receptors. Moreover it has also anti-histaminergic properties.

A recent multicenter Italian study on the use and the self-perceived efficacy and tolerability of pharmacological and non-pharmacological treatments in children and adolescents with migraine suggested that pizotifen and flunarizine were the most effective drugs (82% and 72%, respectively) [72]. Even if pizotifen is the only preventive drug for migraine licensed in Italy for pediatric age, its use is less frequent than flunarizine.

The recommended starting dose is 0.5 mg per day, and may be increased up to 1.5 mg (to be taken in more administrations during the day or once in the evening). Sandomigran is contraindicated in children under 2 years. Very common side effects are increase in appetite and weight increase. Common side effects are sedation (including somnolence), dizziness and nausea.

Tricyclic antidepressants (TCA)

The effectiveness of antidepressant for prophylaxis of migraine in children has been evaluated by few clinical studies. TCA represent the most widely studied antidepressants for migraine prevention.

Amitriptyline (AMI): Amitriptyline is the most used TCA for migraine prevention in children. Its efficacy in pediatric migraine prevention is controversial. Older studies have shown high placebo response rates (up to 50 to 60%) [75-79]. Most recently, a randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg/kg/day), topiramate (2 mg/kg/day) and placebo in children and adolescents 8 to 17 years of age with migraine showed no significant statistically differences in reduction of headache frequency or headache-related disability over a period of 24 weeks, but higher rates of adverse events [80].

A paper presented at the American Academy of Neurology Annual Meeting in New Orleans (2012) showed that amitriptyline was safe and effective for migraine prevention in children and adolescents.

A randomized clinical trial, comparing cognitive behavioral therapy (CBT) plus AMI versus headache education and AMI showed a greater reduction of number of headache days in the CBT plus AMI group [81].

The recommended initial dose of AMI is 0.25-0.50 mg/kg at bedtime to avoid somnolence. It should be titrated slowly over a period of 8-12 weeks, increasing by 0.25 mg/kg/day every 2 weeks [82]. The main side effects include dry mouth, dry eyes, lightheadedness, dizziness, constipation, increased appetite, somnolence, and a prolonged QT at doses of greater than 1 mg/kg. Finally, families should be advised of increased risk of suicidality and should be instructed to notify the physician immediately if this symptom appears [83,84].

Nortriptyline (NOR): Nortriptyline tends to be less sedating than amitriptyline, but there are no well-conducted scientific trials demonstrating the efficacy of nortriptyline.

There is an increased risk of arrhythmia. Dosage is similar, beginning with 10 mg, and escalating to 50-75 mg if tolerated.

Antiepileptics: This class has recently been used in the pediatric migraine prophylaxis. Both topiramate and valproic acid are FDA-approved for prevention of migraine in adults. Furthermore, topiramate was recently approved in adolescents over 12 years of age. Their therapeutic effects in migraine treatment are probably due to their N and T-type calcium channel blocking properties.

Valproic acid: It is considered first-line treatment for adult migraine prophylaxis. Several studies have suggested that valproic acid may be effective in children.

In a small retrospective study comparing the valproic acid with topiramate, both drugs were effective [85]. An open-label safety study focusing on the use of valproic acid in the adolescents migraine prophylaxis found a significant reduction of headache frequency in the first fourth months of therapy [86]. Other retrospective randomized clinical trial comparing the valproic acid with propranolol showed that both drugs were effective, but the mean headache frequency per month was lower in the propranolol group [87]. A recent meta-analysis on the pharmacological preventive treatment of pediatric migraine showed that valproic acid was not effective in reducing the frequency headache [88].

The recommended initial dose of valproic acid is 10-15 mg/kg divided in two daily doses. This dose can be increased with 15 mg/kg increments reaching a maximum dose of 60 mg/kg/day. The most common adverse effects include dizziness, drowsiness, alopecia, weight gain, thrombocytopenia, lymphopenia and elevated pancreatic enzymes. Teratogenic effects must be considered in adolescent females.

Topiramate: Multiple studies showed the effectiveness of topiramate in reducing migraine disability in pediatric population.

In 2014, the FDA approved the use of topiramate for the prevention of headaches in migraine patients aged 12-17 years.

A recent meta-analysis of four randomized placebo-controlled trials on the use of topiramate in the prophylaxis of migraine in patients less than 18 years of age showed that topiramate may both not achieve a more effective clinical trial endpoint than placebo in the prevention of migraines and lead to more side effects or adverse events [89-92]. A recent study comparing topiramate and propranolol showed that topiramate was higher than propranolol group in the reduction of monthly headache frequency, duration attack and disability [93]. According to a recent trial comparing amitriptyline, topiramate and placebo for pediatric migraine [Childhood and Adolescent Migraine Prevention (CHAMP) study], has been showed no significant statistically differences in reduction of headache frequency (52% amitriptyline, 55% topiramate, 61% placebo) or headache-related disability over a period of 24 weeks, but higher rates of adverse events. For this reason, the FDA has given final approval to two supplemental new drug applications (sNDAs) for topiramate extended-release capsule (Qudexy XR, Upsher-Smith Laboratories Inc) to prevent migraine in adults and adolescents aged 12 years and older.

The recommended dose of topiramate is 1-10 mg/kg/day, with a general dose of 50 mg twice per day. The most common side effects include decreased appetite, anorexia, abdominal pain, drowsiness,

paresthesias, cognitive impairment (affecting the verbal fluency, concentration, and working memory). Rarely, hipohydrosis, renal calculi and glaucoma. To avoid significant side effects, particularly cognitive impairment, the dose should be started low and titrated slowly.

Levetiracetam: It is a pyrrolidone derivative with an antiepileptic effect.

A small retrospective review showed a significant reduction of headache frequency from 6.3 to 1.3 headache/month ($p < 0.0001$) in levetiracetam group [94]. Other open label study focusing on the use of levetiracetam in the adolescents' migraine prophylaxis found a significant reduction of headache frequency and disability [95].

The recommended daily dose of levetiracetam is 500-1500 mg twice daily. It has a relatively desirable safety profile, with somnolence, fatigue, irritability, aggressiveness, mild memory and dizziness.

Zonisamide and gabapentin: Few clinical pediatric studies have been performed on the use of gabapentin and zonisamide in migraine prophylaxis.

In a very small retrospective study found that zonisamide is effective in reducing headache frequency (8 of 12 patients) [96]. Other study found that 80% of children treated with gabapentin showed a significant reduction of headache frequency [97].

The recommended daily dose of zonisamide is 100-600 mg per day, while for gabapentin is 300-1200 mg three times daily. The most common adverse effects of zonisamide include dizziness, nausea, irritability and somnolence. The main adverse effects of gabapentin include sedation, ataxia, fatigue and peripheral edema.

Pregabalin: It is an anti-epileptic drug. Pregabalin is commonly prescribed to alleviate nerve or neuropathic pain - a type of pain caused by damage to, or a disease affecting, nerves.

Pregabalin seems to be a well-tolerated and impressive choice for migraine prophylaxis in children. A recent randomized controlled trial showed that pregabalin has been more effective than propranolol: it was associated with a 83.5% decrease in headache frequency and 79.4% decrease in headache severity [98]. In this study, the mean pregabalin dose was 50 mg per day. It is clear that at higher doses more drug side effects may occur.

The main side-effects of pregabalin are drowsiness, dizziness, impaired balance and an inability to think properly. Less common side-effects include blurred vision, dry mouth, fatigue and weight gain.

Botulinum toxin A (BoNT-A)

Botulinum neurotoxin-A (BoNT-A) is a purified neurotoxin complex produced by the anaerobic bacterium *Clostridium botulinum*. The mechanism of action is unknown. Probably, it inhibits the release of migraine related neuropeptides (e.g., CGRP and SP) and glutamate.

According to the 2012 NICE guidelines this treatment is offered to patients failed at least 3 prophylactic therapies. It was approved by the FDA in 2010 for the treatment of chronic migraine in adults. It appears to be effective and well tolerated in adolescents [99,100].

In a retrospective case series of 10 patients with chronic daily headache, treated with 100 units of Onabotulinum Toxin A (OBOT-A), four patients reported improvement in headache, three with decreased frequency and one with only decreased severity [101]. A retrospective review on 45 pediatric chronic daily migraine patients receiving

OBOT-A, showed a reduction of the monthly headache frequency and an improvement in the PedMIDAS score [81]. Most recently, in a small case series of chronic migraineurs (aged 13-17 years), seven of ten patients receiving OBOT-A, showed a good responder rate [102,103].

Main advantages include avoiding side effects of systemic medication, compliance, quicker onset of action than typical slow prophylactic escalation and lack of drug interactions in patients with other medical conditions. The most common adverse events are redness or temporary injection site pain, ptosis and blurred vision.

Calcitonin gene-related peptide (CGRP) and receptor CGRP-r) antibodies

Monoclonal antibodies to calcitonin gene-related peptide and receptor (CGRP and CGRP-r-mAbs) appear more promising for migraine treatment because of considerably better efficacy and safety profiles. A recent meta-analysis suggests the effectiveness of CGRP-mAbs in anti-migraine therapy in adults with few adverse reactions [104,105]. At the moment, there aren't clinical studies in children or adolescents.

Complementary and Alternative Medicine (CAM)

Complementary and alternative medicine may play an important role in the migraine preventive treatment.

The main advantages of non-pharmacological therapy are: the absence of side effects and the best patient and family compliance. Patients prefer this approach to pharmacological therapies for one or more of the following aspects: insufficient or no response to pharmacologic therapy; limited tolerability to drugs, medical contraindications, pregnancy/breastfeeding and the frequent or excessive use of analgesic or acute medications.

These treatments include psychological and behavioral therapies on the one hand and nutraceuticals/supplements on the other.

Psychological and behavioral therapies

Psychological and behavioral treatments include Mindfulness, Cognitive-Behavioral Therapy (CBT), Operant-Behavioural Therapy (OBT), Relaxation and Biofeedback Training or combination of these treatments [106].

Mindfulness has the purpose to teach individuals how to maintain focus on a stimulus while simultaneously allowing intruding thoughts/feelings to be acknowledged, but not judged. Recent studies used mindfulness in a limited group of patients with migraine with encouraging results [107]. In a recent pilot study on mindfulness intervention in adolescents with chronic or episodic high frequency migraine, has been showed a reduction of headache frequency and medication intake and a good feasibility and acceptability of the treatments (although not specifically evaluated) [108].

CBT should be considered the first-line psychological treatment for individuals with chronic pain disorder. Main CBT' indications are the parents' refusal to use drugs, psychiatric comorbidities (such as anxiety, depression, social phobia, performance anxiety), family problems, ineffectiveness or inadequate response to drug therapy [106,109,110]. There aren't rigorous and reliable scientific evidence about CBT and other psychological treatments. A randomized clinical trial looking at children and adolescents with chronic migraine indicated that those patients treated with amitriptyline and CBT

showed a reduction of headache frequency compared to those treated with headache education and amitriptyline [109]. Many other studies, instead, showed a positive effect of CBT on migraine and its psychological comorbidities [106,107,111].

OBT focuses on pain behaviors as a major component of the pain problem, and postulates that they are subject to environmental contingencies. Three therapeutic techniques were shown to be effective: graded activity, activity pacing, and time-contingent medication management [112].

Biofeedback (BFB) Training is a method through which a subject receives information on its autonomic physiological functions (for example heart rate, skin conductance, muscle tone, respiratory rate) through instruments. The BFB training allows to decrease anxiety or improve achievements in short term missions such as sports. According to two recent meta-analyses, biofeedback techniques were highly efficient in management of migraine or tension-type headache in child and adolescent population [113-115].

Nutraceuticals/supplements

Vitamins and supplements could be an attractive option for families who wish to avoid prescription medications and their side effects. Alone or/and in combination, magnesium, riboflavin, coenzyme Q10 and the herbal extracts of butterbur, feverfew and ginkgolide B have all been suggested as preventives for migraine [116]. Although there are only a small number of controlled trials, the results from the CHAMP study may increase the use of these supplements [117].

Magnesium oxide: It is an ion involved in brain excitation. Low levels of magnesium have been found in migraineurs. Few pediatric migraine prevention studies established equivocal results. It is recommended a dose of 400 mg daily. The most common side effect includes diarrhea [118,119].

Riboflavin (vitamin B2): It is a cofactor necessary for mitochondrial oxidation. Low levels of vitamin B2 have been found in migraineurs. There are few and controversial pediatric migraine studies. One randomized, double-blind, placebo-controlled study found that high doses of riboflavin were shown to be initially effective, although this difference was not maintained at 6 months. Other studies showed a high placebo response rate, which complicates interpretation of the results [120-122]. It is recommended a dose of 25-400 mg/day. The most common side effect includes bright yellow urine and diarrhea.

Coenzyme Q10: It is an antioxidant and a cofactor necessary for mitochondrial oxidation. Low levels of Coenzyme Q10 have been found in migraineurs. In a large open-label trial on pediatric migraine supplementation of Coenzyme Q10 showed an improvement of headache frequency and disability scores [123]. It is recommended a dose of 50-100 mg/day. The most common side effect includes nausea, anorexia, dyspepsia, diarrhea.

Vitamin D: Low levels of vitamin B2 have been found in migraineurs. Some studies showed the effectiveness of vitamin D supplementation in reducing headache frequency [124].

Tanacetum parthenium: Feverfew is a derived from a weed plant *Tanacetum parthenium*. It has anti-inflammatory properties. There are not also studies on the efficacy and safety of feverfew in pediatric age [125,126].

Butterbur extract (*Petasites hybridus*): It contains pyrrolizidine alkaloids. It has antispasmodic and anti-inflammatory properties. Two

studies showed an improvement in headache frequency. Side effects are minimal and include burping. It has also a known carcinogenic effect [127,128].

Non-Invasive Neurostimulation

Non-invasive neurostimulation is an innovative strategy for the symptomatic and preventive treatment of migraine and cluster headache, even in episodic form. We remember two procedures.

The first, called non-invasive Vagal Nerve Stimulation (nVNS), consists in the application of a stimulator, called GammaCore, which electrically stimulates the vagus nerve on the lateral cutaneous surface of the neck.

The procedure, when it is used to interrupt the painful attack, consists in applying the stimulator for 2 minutes on both sides of the neck. In preventive use, however, the nVNS is performed 3 times a day, daily, for at least 3 months, each time providing an electrical stimulus lasting 2 minutes on each side of the neck.

The technique is safe and generally well tolerated. The nVNS has been shown to significantly influence the activity of glutamate in the trigeminal nucleus, a key center for the propagation of headaches.

In a recent Italian study non-invasive the nVNS used for the acute treatment of migraine without aura in adolescents, showed a favorable safety and tolerability. This option is able to reduce the number of medication for aborting attacks in this particular and sensitive category of patients where options without side effect are suitable [129].

Additional studies with larger population of patients and sham condition are warranted.

Other non-invasive neurostimulation technique is the Transcranial Magnetic Stimulation (TMS). In a recent review about non-pharmacological approaches for headaches in young age it was investigated the efficacy of single-pulse TMS in adolescents with chronic migraine. During the 12 week treatment period, patients were instructed to use the device twice daily: a significant reduction in headache frequency (33.8%) was found [130].

Discussion

Migraine in pediatric population, as well as in adults, is often unrecognized or misattributed to secondary causes such as sinus disease or emotional disorders. A detailed anamnesis is a very important component of diagnosis. It takes a lot of time and practical experience. History-taking consists in having the right suspicions, asking the right questions in the right sequence to arrive at the right diagnosis and initiate the right treatment [131].

In the literature, data on the current clinical practice on treatment of pediatric migraine are very limited.

We evaluated the use of acute and preventive drugs, nutraceuticals and non-pharmacological treatments.

Acute or symptomatic treatment is always more effective when given early during the attack. NSAIDs, especially ibuprofen, should be preferred to acetaminophen for treating acute attacks of migraine, because they were usually more effective and well tolerated. If NSAID are not effective, triptans could be used more frequently as first for treating migraine attack in adolescents.

Migraine prophylaxis includes a large number of drugs but relatively few rigorous, randomized controlled studies have been carried out in children and adolescents. According to the main guidelines or systematic reviews for preventive treatment of paediatric migraine flunarizine is recognized as the first choice drug for prophylaxis, followed by propranolol, amitriptyline, pizotifen, cyproheptadine and antiepileptic drugs (topiramate and valproate).

As concerns preventive treatments, further studies on nutraceuticals are necessary in particular to establish mechanisms of action of the molecules contained in these multiple compounds and their efficacy.

Therefore, the use of non-pharmacological preventive treatments (i.e. relaxation techniques, biofeedback, cognitive-behavioral therapy) should be implemented in clinical practice, especially in cases with contraindications or poor tolerability or efficacy to preventive drugs. The combination of behavioral approaches with pharmacological therapies has been shown to be superior to each individually and appear to maximize long-term efficacy [132].

Finally, according to the National Headache Foundation a correct management of headache includes writing and keeping a headache diary. It is very important in keeping detailed records of headache episodes, identifying trigger factors (avoiding them) and defining patterns migraine to begin the most effective treatments [133].

Conclusions

The treatment of pediatric migraine is multidisciplinary. It includes lifestyle changes (nutrition, stress, sleep, physical activity,...), symptomatic and preventive pharmacological therapies, non-pharmacological preventive therapies (psychological and behavioral therapies, nutraceuticals) and compilation of the headache diary.

Pediatric RCTs, based on larger samples sizes and innovative study protocols, involving multicenter studies and primary care services (to reduce selection bias), are needed to better understand the most effective and safe treatment strategies for pediatric migraine patients and define "responders" profile.

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