Pediatric Migraine Treatment: An Updated Review

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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 ClassiŽcation of Headache Disorders, 3rd edition. Headache ClassiŽcation Committee of the International Headache Society (IHS) classiŽed 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].

The diagnosis is based on clinical criteria established by the International ClassiŽcation 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

T is 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. T e 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

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)		

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

Total (95% CI)	171	174	1.67 [1.00, 5.23]

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					
Hamalainem 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) Total events	259	933	50	599	1.66 [1.16, 2.38]
Total (95% CI)	1300	4250	577	2511	1.32 [1.19, 1.47]

reduction in headache frequency, but did not found a signiŽcant statistically di f erence between proponolol and valproate [61,62]. Equal e f cacy in reducing of headache frequency has been found in an open, randomized comparison of propanolol and cinnarizine [63]. Propranolol e f cacy in reducing the frequency and duration of pediatric migraine headache has been compared with pregabalin: a signiŽcant di f erence between these two groups was found [64].

All these studies have suggested the e f cacy of propanolol 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 e f ects 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 lossa, 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
Propanolol	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

paresthesias, cognitive impairment (afecting the verbal ẑuency, concentration, and working memory). Rarely, hipohydrosis, renal calculi and glaucoma. To avoid signiẐcant side efects, particularly cognitive impairment, the dose should be started low and titrated slowly.

Levetiracetam: It is a pyrolidone derivative with an antiepileptic efect.

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 ûunarizine is recognized as the Ûrst choice drug for prophylaxis, followed by propanolol, amitryptiline, 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 e f cacy.

T erefore, 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 e f cacy to preventive drugs. T e combination of behavioral approaches with pharmacological therapies has been shown to be superior to each individually and appear to maximize long-term e f cacy [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 deŽning patterns migraine to begin the most e fective treatments [133].

T e 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 e fective and safe treatment strategies for pediatric migraine patients and deŽne “responders” proŽle.

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