

# Pediatric Migraine

By Pediatric neurology of Chiayi  
Christian Hospital

Dr. 林高民

# Case presentation

	age (years)	sex	time (years)	frequency	lasting duration	location
case 1	12	female	5-6	3-6/week	1/2-2 days	bitemporal
case 2	14	female	2	daily recently	1/2-1 days	bitemporal

	characteristics	severity (self score)	avoid routine activity	nausea/vomiting	photophobia/ phonophobia
case 1	throbbing	7-8	不想動	vomiting	phonophobia
case 2	tightness or throbbing	8-9	躺床上	vomiting	phonophobia

	NE	optic disc	blood pressure (mmHg)	Neuroimage	acute infusion	sleep partially resolved
case 1	unremarkable	normal	109/66	N	N	Y
case 2	unremarkable	Normal	119/79	N	Mannitol	Y

	prophylactic oral medications	outcome severity	outcome frequency	predisposed factor
case 1	inderal(40) 1/2# bid	4-5	3/month	N
case 2	tryptanol 1# qn	3	4-5/moth	基測

# Epidemiology

- First report: Bille in 1962
- 75% children have a notable headache by 15 y/o
- Migraine: 3.9% of 7-15 y/o  
1.7% in 7 y/o to 5.3% in 15 y/o

*Acta Paediatrica Suppl 1962; 136: 16-151*

Age (Mean  $\pm$  SD, min-max) 8.2  $\pm$  2.4 (5.0-13.0)

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	n	%
Sex		
Girl	1354	51.0
Boy	1303	49.0
Total	2657	100.0
SES		
Low	173	7.4
Medium low	613	26.4
Medium	763	32.8
Medium high	511	22.0
High	263	11.3
Total	2323	100.0
The presence and the type of headache		
Non-headache	1437	53.8
Migraine	92	3.4
Probable migraine	231	8.7
Non-migraine headache	909	34.1
Total	2669	100.0
Family history of headache†		
No	1138	57.9
Yes	828	42.1
Total	1966	100.0
Passive smoking		
No	606	28.8
Yes	1500	71.2
Total	2106	100.0

Variable	n	OR	95% CI	P value
Any headache in the last 3 months	2465			
Frequent headache		4.6	2.6-8.4	<.001
The presence of migraine or probable migraine		2.4	1.2-4.6	.013
High depression score		3.6	2.0-6.5	<.001
Headache intensity (reference: mild intensity)				.005
Moderate		2.0	1.0-4.0	.051
Severe		4.1	1.8-9.5	.001
Migraine or probable migraine	928 23.4%			
Frequent headache		5.2	2.7-10.3	<.001
High depression score		3.1	0.7-3.7	.001
Headache intensity (reference: mild intensity)				.009
Moderate		1.6	0.7-3.7	.311
Severe		4.1	1.6-10.6	.004
Tension-type headache	1092			
High depression score		19.8	4.3-90.3	.001

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# Pathophysiology- Genetics

- *CACNA1A* (Ca channel)
- *ATP1A2* (Na/K pump)
- *SCN1A* (Na channel): familiar hemiplegic migraine
- Chromosome 14q32
- Serotonin transporters gene
- *KCNN3* (K channel)
- 5,10-methylenetetrahydrofolate (MTHFR)
- Angiotension-converting enzyme
- Matrix metalloproteinase 3

# Pathophysiology- Biological changes

- No biological markers
- increase: Interleukin-1 $\alpha$   
sTNF receptor 1  
TNF  
calcitonin gene-related peptide
- Decreased: coenzyme Q10



**Table 2** P100 latency and amplitude (mean  $\pm$  SD)

	Migraine	Tension headache	Control
Latency (ms)	103.94 $\pm$ 5.09	101.03 $\pm$ 4.19	100.62 $\pm$ 3.67 <sup>†</sup>
Amplitude ( $\mu$ V)	11.9 $\pm$ 1.5	10.8 $\pm$ 1.2	10.3 $\pm$ 0.9 <sup>‡</sup>

<sup>†</sup>Significant difference between migraine and other two groups,  $P = 0.008$  for migraine vs control group and  $P = 0.028$  for migraine versus tension headache group.

<sup>‡</sup>Significant difference between migraine and other two groups,  $P = 0.009$  for migraine vs control group and  $P = 0.031$  for migraine versus tension headache group.

**Table 4** Brainstem auditory evoked potentials (mean  $\pm$  SD)

	Migraine	Tension headache	Control
Wave I (ms)	2.51 $\pm$ 0.21	2.46 $\pm$ 0.17	2.44 $\pm$ 0.14 <sup>†</sup>
Wave III (ms)	4.57 $\pm$ 0.18	4.53 $\pm$ 0.15	4.51 $\pm$ 0.15 <sup>†</sup>
Wave V (ms)	6.45 $\pm$ 0.19	6.39 $\pm$ 0.20	6.35 $\pm$ 0.17 <sup>†</sup>
Interpeak latency I–III (ms)	2.06 $\pm$ 0.19	2.07 $\pm$ 0.20	2.07 $\pm$ 0.15 <sup>†</sup>
Interpeak latency III–V (ms)	1.88 $\pm$ 0.21	1.86 $\pm$ 0.18	1.84 $\pm$ 0.15 <sup>†</sup>
Interpeak latency I–V (ms)	3.93 $\pm$ 0.21	3.93 $\pm$ 0.18	3.91 $\pm$ 0.16 <sup>†</sup>

*P* > 0.05.

**TABLE 1. International Headache Society Classification of Migraine (ICHD-II)**

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- 1) Migraine without aura
- 2) Migraine with aura
  - a. Typical aura with migraine headache
  - b. Typical aura with non-migraine headache
  - c. Typical aura without headache
  - d. Familial hemiplegic migraine
  - e. Sporadic hemiplegic migraine
  - f. Basilar-type migraine
- 3) Childhood periodic syndromes that are commonly precursors of migraine
  - a. Cyclic vomiting
  - b. Abdominal migraine
  - c. Benign paroxysmal vertigo of childhood
- 4) Retinal migraine
- 5) Complications of migraine
- 6) Probable migraine

# Diagnostic criteria- Migraine without aura

## *Diagnostic criteria*

- A At least five attacks\* fulfilling criteria B–D
- B Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)† ‡ §
- C Headache has at least two of the following characteristics:
  - 1 Unilateral location¶ ||
  - 2 Pulsating quality\*\*
  - 3 Moderate or severe pain intensity
  - 4 Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D During headache at least one of the following:
  - 1 Nausea and/or vomiting
  - 2 Photophobia and phonophobia††
- E Not attributed to another disorder‡‡

# Pediatric migraine

TABLE 2. Migraine Without Aura in Children (ICHD-II Diagnostic Criteria)

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- A) At least 5 attacks fulfilling criteria B-D
- B) Headache attacks lasting 1-72 hrs
- C) Headache has at least 2 of the following characteristics:
  - i) unilateral or bilateral
  - ii) pulsating quality
  - iii) moderate or severe pain intensity
  - iv) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D) During headache at least one of the following:
  - i) nausea and/or vomiting
  - ii) photophobia and phonophobia
- E) Not attributed to another disorder

# Characteristics of pediatric migraine

- Short duration
- Sleep should be included as part of duration
- More likely to be bilateral (frontal-temporal)
- Photophobia and phonophobia by child's action
- **Occipital** location should be further assessment

*Lancet Neurology 2010; 9: 190-204*  
*Curr Opin Neurol 2010 Jun;23(3):249-53*

- More description of **tightness pain**

# Difficulties in young children

- Poor detail descriptions
- Anxiety of parents
- Brain tumor, esp. posterior fossa
- Frequent head hitting
- Uncooperative to PE and NE
- Lost follow-up
- Psychological interference

1. How many full school days of school were missed in the last 3 months due to headaches? \_\_\_\_\_

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)? \_\_\_\_\_

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)? \_\_\_\_\_

4. How many days were you not able to do things at home (i.e., chores, homework, etc.) due to a headache? \_\_\_\_\_

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)? \_\_\_\_\_

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)? \_\_\_\_\_

**Total PedMIDAS Score** \_\_\_\_\_

**Headache Frequency** \_\_\_\_\_

**Headache Severity** \_\_\_\_\_

# PedMIDAS: migraine disability assessment



# Associated symptoms

- Osomophobia: sensitive and specific from TTH
- Cutaneous allodynia

*Lancet Neurology 2010; 9: 190-204*  
*Curr Opin Neurol 2010 Jun;23(3):249-53*

# Further Assessment

- Children difficult to obtain accurate responses
- Parental responses by their own experiences
- Children's drawings

*Lancet Neurology 2010; 9: 190-204*  
*Curr Opin Neurol 2010 Jun;23(3):249-53*

# Examination

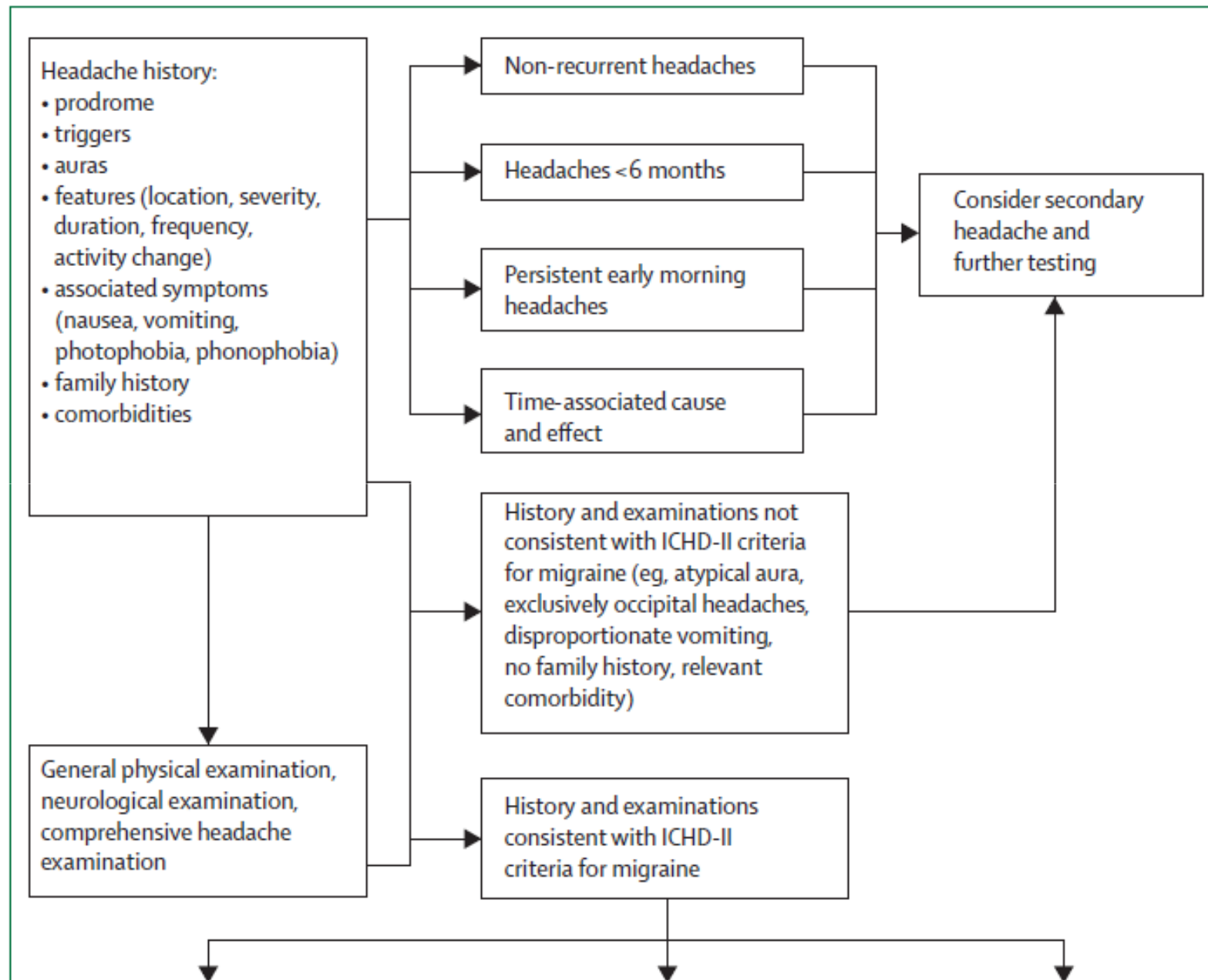
- Complete history
- General examination
- Neurological examination
- Neck tenderness and stability
- Stability of temporomandibular joint
- Sinus and facial tenderness
- General cranial palpation
- Muller's sign

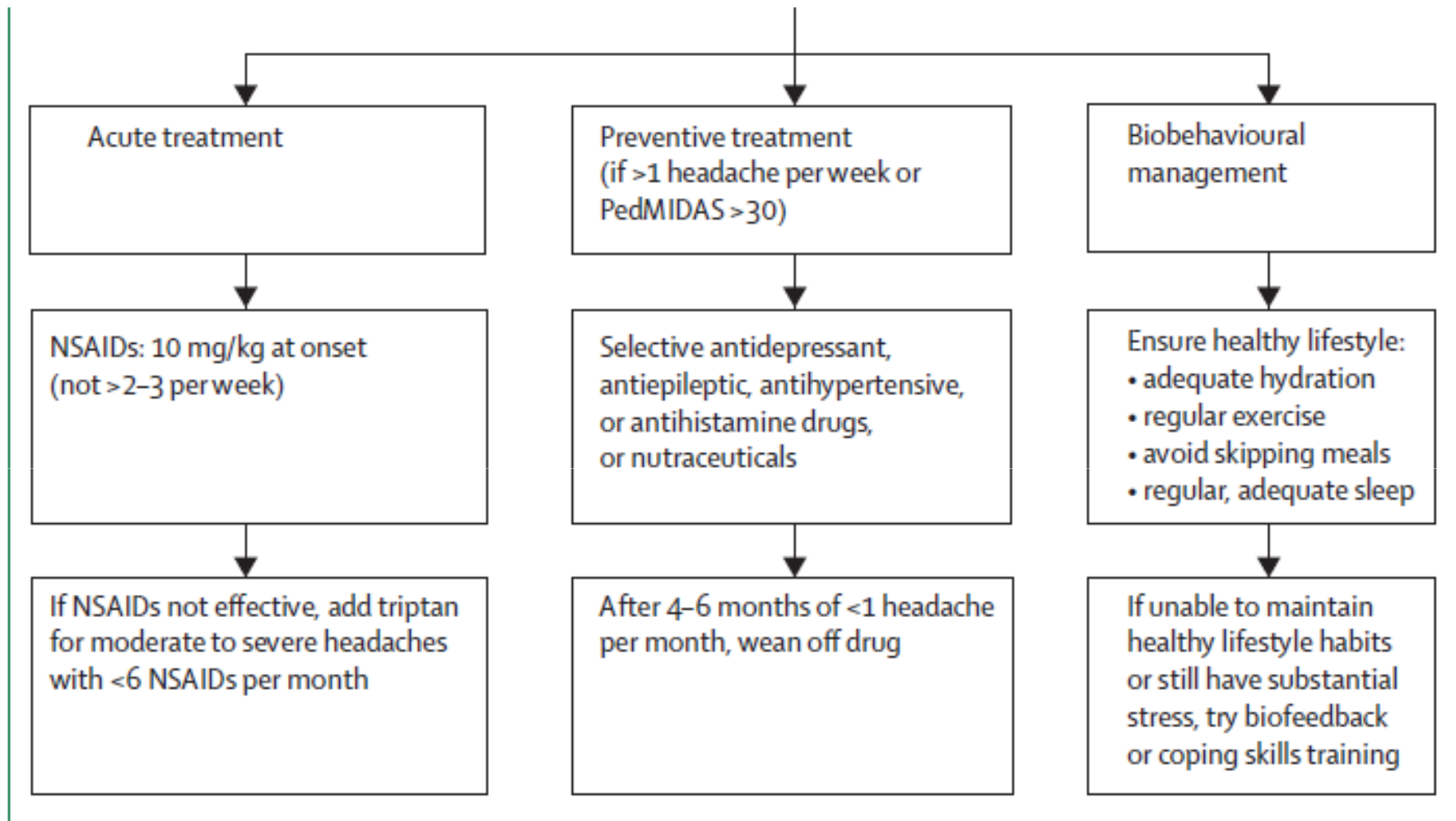
# Differential Diagnosis

- Sinus headache: Muller's sign
- Moyamoya disease
- Psychological problems: school phobia and anxiety

# Neuroimaging

- **Neurological examination** is the most sensitive test to identify the need for neuroimaging.
- Need: occipital location (posterior fossa tumor)
- No need: long standing  
recurrent  
do not change with a normal NE





*Lancet Neurology 2010; 9: 190-204*

# Acute treatment

- NSAID (Ibuprofen): 7.5-10mg/kg/dose
- Triptans: more severe

Almotriptan by FDA

nasal sumatriptan and zolmitriptan by EMEA

*Lancet Neurology* 2010; 9: 190-204

*CNS Drugs* 2006; 20(10): 813-820



# Prophylactic Medications

- Antihistamine: cyproheptadine
- Antidepressants: Amitriptyline, Nortriptyline, Duloxetine
- $\beta$ -blockers: propranolol
- Calcium channel blockers: verapamil
- Anticonvulsants: Topiramate, Valproic acid

**Table 3** Symptomatic drugs evaluated in placebo-controlled and open clinical trials

Drug	Evidence level	Study design	Ages (years)	<i>n</i>	Primary end point: pain relief (hours)	Responders (%)	Placebo responses (%)	<i>P</i> value	Author/Pubdate/Ref.
<b>Ibuprofen</b>									
10 mg/kg	A	rDBPC	4–16	88	2	68	37	<0.05	Hamalainen et al., 1997 [10, 16]
7.5 mg/kg		DBPC	6–12	84	2	76	53	0.006	Lewis et al., 2002 [10, 16]
200–400 mg		DBPCCO	6–18	32	2	69	28	<0.05	Evers et al., 2006 [21]
<b>Acetaminophen</b>									
15 mg/kg	B	rDBPC	4–16	88	2	54	37	<0.05	Hamalainen et al., 1997 [10, 16]
<b>Sumatriptan nasal</b>									
20 mg	A	rDBPC	6–10	14	2	86	42.8	0.03	Ueberall et al., 1999 [18]
5–10–20 mg		rDBPC	12–17	510	2	63–66	53	<0.05	Winner et al., 2000 [18]
10–20 mg		rDBPCCO	8–17	83	2	64	39	0.003	Ahonen et al., 2004 [18]
20 mg		rDBPC	12–17	738	1	61	52	ns	Winner et al., 2006 [19]
<b>Sumatriptan oral</b>									
50–100 mg	C	rDBPCCO	8–16	23	2	30	22	ns	Hamalainen et al., 1997 [10, 16]
<b>Sumatriptan subcutaneous</b>									
3–6 mg	C	OL	6–16	17	2	64	–	–	MacDonald, 1994 [10, 16]
0.06 mg/kg		OL	6–18	50	2	78	–	–	Linder, 1996 [10, 16]

**Table 3** Symptomatic drugs evaluated in placebo-controlled and open clinical trials

Drug	Evidence level	Study design	Ages (years)	<i>n</i>	Primary end point: pain relief (hours)	Responders (%)	Placebo responses (%)	<i>P</i> value	Author/Pubdate/Ref.
Zolmitriptan oral									
2.5–5 mg	C	OL	12–17	38	2	88	–	–	Linder et al., 2000 [10, 16]
2.5 mg		DBPCCO	6–18	32	2	62	28	<i>P</i> < 0.05	Evers et al., 2006 [21]
2.5–5–10 mg		rDBPC	12–17	850	2	53–57	58	ns	Rothner et al., 2006 [20]
Zolmitriptan NS									
5 mg	B	SB-DBPC	12–17	171	1	58.1	43.3	<i>P</i> < 0.05	Lewis et al., 2007 [22]
Rizatriptan oral									
5 mg	C	rDBPC	12–17	296	2	66	56	ns	Winner et al., 2002 [10, 16]
5 mg		rDBPC	12–17	234	2	68.2	68.8	ns	Visser et al., 2004 [23]
5 mg		OL	12–17	686	2	77	–	–	Visser et al., 2004 [23]
5–10 mg		rDBPC	6–17	96	2	74	36	<i>P</i> = 0.001	Ahonen et al., 2006 [24]
Almotriptan oral									
6.25–12.5 mg	B	OL	11–17	15	2	85	–	–	Charles et al., 2006 [25]
6.25–12.5–25 mg		rDBPC	12–17	866	2	67–73	55	<i>P</i> < 0.001	Linder et al., 2008 [26]
Eletriptan oral									
40 mg	C	DBPC	12–17	267	2	57	57	ns	Winner et al., 2007 [27]
Naratriptan oral	C	DBPC	12–17	300	4	64–72	65	ns	Rothner et al., 1997 [10, 16]

*DBPC* double-blind placebo-controlled, *DBPCCO* double-blind placebo-controlled crossover, *rDBPC* randomized double-blind placebo controlled, *HA* headache, *OL* open-label, *RR* retrospective review

**Table 4** continued

Drug	Evidence level	Study design	Ages (years)	<i>n</i>	Drug response rate (%)	Placebo response rate (%)	<i>P</i> value (primary endpoint)	Reference
Flunarizine								
5 mg	A	DBPC	7–14	42	76	19	<i>P</i> < 0.001 (freq and durat)	Sorge et al., 1985 [1, 10]
5 mg		OL	10–13	12	66	–	–	Guidetti et al., 1987 [1, 10]
5 mg		DBPC CO	5–11	63	67	33	<i>P</i> < 0.001 (freq) <i>P</i> < 0.01 (durat)	Sorge et al., 1988 [1, 10]
Nimodipine								
10–20 mg	C	DBPCCO	7–18	37	15	15	ns (freq)	Battistella et al., 1990 [1, 10]
Propranolol								
60–120 mg	C	DBCO	7–16	28	82	14	<i>P</i> < 0.001 (freq)	Ludvigsson et al., 1974 [1, 10]
80 mg		DBPC	3–12	39	58	55	ns	Forsythe et al. 1984 [1, 10]
3 mg/kg		DBPC	6–12	28	ns	ns	ns	Olness et al., 1987 [1, 10]
Timolol	C	DBPC CO	6–13	19	38	40	ns	Noronha et al. 1985 [1, 10]
Clonidine								
25–50 µg	C	DBPC	<15	57	32	34	ns	Sillanpaa, 1977 [1, 10]
0.07–0.1 mg		DBPC	7–14	43	ns	ns	ns	Sills et al., 1982 [1, 10]
Cyproheptadine								
4 mg	C	RR	3–12	30	83	–	–	Lewis et al., 2004 [32]
Amitriptyline								
1 mg/kg	C	OL	9–15	192	84	–	–	Hershey et al., 2000 [1, 10]
10 mg		RR	3–18	73	89	–	–	Lewis et al., 2004 [32]

Table 4 continued

Drug	Evidence level	Study design	Ages (years)	<i>n</i>	Drug response rate (%)	Placebo response rate (%)	<i>P</i> value (primary endpoint)	Reference
Trazodone								
1 mg/(kg day)	C	DBPC	7–18	35	45	40	ns	Battistella et al., 1993 [1, 10]
Pizotifen	C	DBPC CO	7–14	47	15	16	ns	Gilles et al., 1986 [1, 10]
Topiramate								
12.5–225 mg	A	OL	8–15	75	43–59	–	<i>P</i> < 0.001 (freq)	Hershey et al., 2002 [1, 10]
2–3 mg/kg		rDBPC	6–15	162	54.6	46.9	ns	Winner et al., 2005 [35]
50, 100, 200 mg		DBPC	12–17	51	46–65	16	<i>P</i> = 0.02 (100 mg), <i>P</i> = 0.04 (200 mg) (freq)	Winner et al., 2006 [38]
100 mg		DBPC	8–14	44	95	52	<i>P</i> = 0.02 (freq)	Lakshmi et al., 2007 [36]
100 mg		rDBPC	12–17	85	83	45	<i>P</i> < 0.001 (freq)	Lewis et al., 2009 [37]
50–200 mg		RR	7–20	37	76	–	<i>P</i> < 0.001 (freq)	Cruz et al., 2009 [39]
Valproate								
15–45 mg/ (kg day)	B	OL	7–16	42	78.5	–	<i>P</i> < 0.05 (freq)	Caruso et al., 2000 [1, 10]
500–1,000 mg/ day		OL	9–17	10	83	–	<i>P</i> = 0.002 (freq)	Serdaroglu et al., 2002 [1, 10]
250–1,125 mg/ day		OL	7–17	23	65	–	<i>P</i> < 0.05 (freq)	Pekalnis et al., 2001 [1, 10]
10–40 mg/ (kg day)		rDBPC	3–15	58	72	–	<i>P</i> < 0.05 (freq)	Ashrafi et al., 2005 [40]
250, 500, 1,000 mg		rDBPC	12–17	300	36–51	46	ns	Apostol et al., 2008 [41]
500–1,000 mg		OL	12–17	241	–	–	>75% (freq)	Apostol et al., 2009 [42]
Levetiracetam								
250–1,500 mg	B	OL	19	3–17	52	–	<i>P</i> < 0.001 (freq)	Miller et al., 2004 [1, 10]
		OL	20	6–17	90	–	<i>P</i> < 0.001 (freq)	Pekalnis et al., 2007 [44]

**Table 1.** Triptans in the pediatric population: formulations, pharmacokinetics, dose, efficacy, tolerability, and cost<sup>[11-51]</sup>

Medication and formulation	Pediatric dose in mg (bodyweight or weight-adjusted dose) [age]	Maximum dose/day (mg)	Studied efficacy	Adverse effects (incidence; formulation)	Pharmacokinetics (patient age and study reference)	Cost (\$US) <sup>(11) a</sup>	Data available to support use in children (age group)
<b>Sumatriptan<sup>[12-31]</sup></b>							
Nasal	5, 20 (>40 kg) [12-17 y]	40	+/-	Bad taste <sup>b</sup> (13-30%; nasal); warmth, tingling, burning sensation (nasal, SC); sense of pressure (SC); injection site reactions (SC); vomiting, nausea (nasal, SC, oral)	Similar to adults (8-11 y, <sup>[30]</sup> adolescents <sup>[31]</sup> )	34.71	Yes (>5 y)
SC	4, 6 (0.06 mg/kg/dose)	12	+			81.62	Yes (>6 y)
Oral	25, 50, 100 [8-17 y] <sup>c</sup>	200	-			22.88	No
<b>Rizatriptan<sup>[32-37]</sup></b>							
Oral tablet	5 (20-39 kg) 10 (>40 kg)	30 <sup>d</sup>	+/-	Dizziness, dry mouth, asthenia, somnolence, nausea	Similar to adults (12-17 y <sup>[37]</sup> )	21.06	Yes (>6 y)
Oral disintegrating	5 [12-17 y]		+			21.06	Yes (>6 y)
<b>Zolmitriptan<sup>[38-43]</sup></b>							
Oral	2.5, 5, 10 [12-17 y]	10	+/-	Tightness, dizziness, nausea, paresthesia, asthenia, pain, headache, non-chest tightness, somnolence (oral, nasal), taste disturbance (6.5%, nasal), nasal discomfort (nasal), congestion (nasal)	Shorter t <sub>1/2</sub> in adolescents compared with adults (mean 14.5 y <sup>[42]</sup> )	20.07	Yes (>12 y)
Nasal	5 [12-17 y]	10	+			29.25	Yes (>12 y)

# Non-pharmacologic treatment

- Nutraceuticals: coenzyme Q10, butterbur, riboflavin, magnesium
- Biobehavioural therapy

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Thank you!