



Treatment of migraine in children and adolescents. The state of the art

Renato Arruda , Marco Antônio Arruda 

Glia Institute, Ribeirão Preto, São Paulo, Brazil



Marco Antônio Arruda
arruda@institutoglia.com.br

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Marcelo Moraes Valença

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Abstract

Introduction

Headaches and migraine are common in the pediatric population, being one of the most frequent symptoms reported in practice. Additionally, it is a considerably disabling condition, which brings significant burden and impairs several aspects of a child or adolescent's life, such as mental and physical health, executive functioning, school performance. Children and adolescents with migraine have higher risk of psychiatric comorbidities and psychosocial adjustment difficulties, which, in turn, compromise even more patient's well-functioning.

Objective

The present article provides the clinician with a straightforward and evidence-based approach to migraine treatment in this age group.

Comment

Treatment of migraine in children and adolescents requires a systematic and thorough approach. Clinicians should keep in mind the important burden migraine brings to a child's life, thus investigate, and properly manage comorbidities presented. Patient and parents' education is a meaningful part of the treatment. Moreover, non-pharmacological treatments, such as healthy lifestyle habits, behavioral interventions may also play beneficial roles. When preventive treatment is indicated, it should be tailored considering drug's profile of effectiveness and safety, as well as patient's comorbidities. Lack of evidence in this context must not translate in lack of action by the clinician, since there may be a relevant burden associated. Therefore, reasoning for the perspicacious clinician is of fundamental importance and may influence positively the outcomes.

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Introduction

Headache is one of the most frequent symptoms that brings a child or adolescent to a neurologist or pediatric clinic. According to the 2017 Global Burden of Diseases, Injuries and Risk Factors (GBD) study, there were more than 700 million people between 5-19 years suffering from migraine or tension-type headache (TTH). Together, these conditions accounted for almost 40% of all-cause prevalence in children and adolescents.^{1,2}

Not only prevalent, but also considerably disabling. Migraine carries a remarkable burden to the child or adolescent suffering from it, besides causing a substantial impact on several aspects of the patient's life.³⁻¹²

Accordingly, migraine treatment in the pediatric population requires a systematic and thorough approach. Despite the discussions involving the findings of clinical trials on pediatric migraine, in the clinical practice, pharmacological or non-pharmacological treatment, patient and parents' education about migraine, as well as the identification and management of comorbidities are of fundamental importance and makes significant difference in the outcomes of such disease in this age group.

Burden

There is a growing body of evidence, derived from clinical and population studies using validated instruments, showing a critical burden of migraine in the school functioning (academic performance, academic competence perception and social and school activities participation)³⁻⁶, quality of life⁵⁻⁷, mental health⁸⁻¹¹ and family dynamics.^{5,12}

Comparing the quality of life of 2,500 children suffering from the ten most prevalent pediatric chronic diseases, those with migraine had one of the worst average scores, below cerebral palsy, mental disorders and asthma.¹³ A significant amount of this burden is due to psychiatric comorbidities of migraine in childhood and adolescence.

Psychiatric Comorbidity and Psychosocial Adjustment

Clinical¹⁴⁻¹⁹ and population studies^{9,20,21} reveal that children and adolescents with migraine present a higher prevalence of anxiety and depression symptoms, compared with controls without headache. More recent studies point to a comorbidity of migraine with the Attention-Deficit and Hyperactivity Disorder (ADHD) in children²², adolescents²³ and adults.²⁴ Moreover, the former study identified a significant association between headache frequency and risk of ADHD. Compared to children with less than 4

headache attacks per month, those with 10 or more had a 11-fold higher risk of comorbidity with ADHD.²² Other determinant factors of the psychiatric comorbidity in childhood migraine are intensity, duration, frequency of headache, presence of nausea, and medication-overuse.⁹

Utilizing a specific instrument for the assessment of psychosocial adjustment - the *Strengths and Difficulties Questionnaire* (SDQ)^{17,25}, a population study showed that children with migraine have a higher risk of presenting emotional symptoms, conduct problems, hyperactivity, and problems with colleagues than those with TTH and those without headache. Children with TTH have a higher risk of emotional symptoms than controls without headache. Inferred by logistic regression analyses, the determinants of chronic headache burden on psychosocial adjustment were: frequency of headache, presence of nausea, photo and phonophobia during the attacks, pre-natal exposition to tobacco, and poor school performance.⁸

As stated, children and adolescents with migraine have a higher risk of psychiatric comorbidity and psychosocial adjustment, mainly those with chronic migraine. Whenever these comorbidities or even difficulties are not identified or treated properly, the efficacy of the headache or migraine treatment is considerably impaired. Therefore, the child neurologist should proceed to investigate such comorbidities and difficulties in every child or adolescent who presents with recurrent headache.

Assessment of Psychiatric Comorbidity and Psychosocial Adjustment

In this approach, we indicate an instrument for psychosocial adjustment problems triage, the SDQ. It is validated for application in children from 4- to adolescents until 16-years-old and have several versions that can be fulfilled by the parents, teachers or adolescents. For routinely clinical purpose, we recommend the parents version, translated to the Brazilian Portuguese and of public domain (www.sdqinfo.org). Composed by five scales, each of them containing five items that evaluate emotional symptoms, conduct problems, hyperactivity/inattention, problems with colleagues and behavioral problems. The parents answer their version and the impact supplement, which assess the chronicity and burden of these difficulties in various contexts of the child's life. Such information is of great importance to the diagnosis of psychiatric comorbidities, according to the DSM-5 criteria.²⁵ Even though it has not been standardized in a Brazilian sample, the utilization of the North American



standard is useful in daily clinical practice. Whenever is needed to deepen this investigation or when the suspicion of psychiatric comorbidity is strong, we advise the application of the parents' version of the *Child Behavior Checklist (CBCL)*.²⁶

Whenever there is a suspicion of ADHD, the search for the symptoms associated can be done by the MTA-SNAP-IV Questionnaire²⁷, fulfilled by the parents and teacher(s) of the child or adolescent. This questionnaire captures inattention, hyperactivity and impulsivity symptoms based on DSM-5 criteria.²⁵

Executive Functions

Executive functions (EF) are a set of mental processes which regulate the cognition, emotions and behavior, with the aim of performing actions in the present or accomplishing objectives in the future.^{28, 29} Soaring amount of evidence suggest that EF have a critical role in developmental psychopathology³⁰⁻³², with clinical and subclinical manifestations and a plausible neurobiological basis.³³ EF also have a direct correlation with school performance, being a predictor of reading and mathematical skills more relevant than the intelligence quotient.³⁴⁻³⁶

Given the evidence of psychiatric comorbidity and poorer school performance in children and adolescents with migraine, in relation to those without headache, it is plausible to consider the possibility of the EF being mediators of these associations. Accordingly, from a population sample of 399 adolescents between 10- and 18-years-old, validated instruments were applied to assess psychosocial adjustment (SDQ) and EF (Executive Functions Inventory for Children and Adolescents, EFICA).³⁷ In relation to adolescents without headache, those with episodic migraine had a significant higher risk of worse executive functioning (RR = 3.5, CI 95% 1.2-10.1). Adolescents with high frequency headache (≥ 10 attacks per month) also had a higher risk of executive dysfunction (RR = 4.9, CI 95% 1.2-20.6).³⁸

Another recent study, applying neuropsychological tests in a group of adolescents with migraine, chosen in a tertiary headache clinic, found an inferior performance in short- and long-term verbal memory, attention, EF and processing speed, compared with those without headache.³⁹

The cognitive impairment in patients with migraine during the attacks has been described in the literature by clinical studies with adults. Nevertheless, the above-mentioned evidence of executive dysfunction in the interictal period,

collected with different methodologies, and from populational and clinical samples, embodies initial data of a possible mediation of EF in psychiatric comorbidity and poor academic performance observed in children and adolescents with migraine.

School Functioning

The burden of migraine over school functioning has been documented. A recent binational population study revealed that 20.7% of children and adolescents who had chronic headache had lost at least one school day over the last four weeks before the survey due to headache; 48.8% reported at least one school day impaired activities over the same period due to headache.⁵

A population study with 5,671 Brazilian children showed a significant burden of migraine in school performance and absenteeism. Compared with children without headache, those with episodic migraine presented a 1.3 times higher risk of poor academic performance, and those with chronic migraine, a 1.6 times higher risk. Multivariate analysis demonstrated the factors significantly influencing the poor academic performance, which were: intensity, duration and frequency of attacks, nausea, abnormal mental health scores, medication-overuse and male gender. Compared to children with TTH, those with migraine had a significant higher risk of absenteeism and being dismissed of school due to headache. The absenteeism was significantly influenced by the intensity and duration of attacks, occurrence of nausea and medication-overuse.⁴

The findings cited above have clinical importance, since they enlighten migraine's and children's characteristics that increases the risk of impact on school functioning, quality of life and presence of psychiatric comorbidities.

Trigger Factors

It is common that some triggers might be mistaken as exacerbating factors, and this difference has clinical importance. For instance, if the physical activity triggers the headache attacks, the possibility of vascular malformations or aneurysms should be considered. Differently, during a headache attack, the exacerbation of headache by the physical activity is characteristic of migraine.

The identification of triggers may elucidate the causes of many of secondary headaches from ICHD's groups 5 to 12. For primary headaches like migraine and TTH, the following situations may occur: a) one or more triggers are identified, sometimes acting separately,



sometimes simultaneously; b) triggers may or may not cause headache attacks every time there is the exposure; c) a specific trigger may change its behavior in different periods of life (it triggered the headache attacks during a life period, but it might not trigger anymore in other periods); and, d) no triggers are identified.

The literature describes several well-known triggers of migraine: negative and positive emotions, excess or sleep deprivation, sun exposure or stroboscopic effect, noise, smells, food, fasting, menstruation, physical activity, temperature changes, traumatic brain injury, travels, etc.^{40, 41}

Some foods may trigger migraine attacks, but, eventually, they might be the specific and unique cause of a determined headache. This condition was named as headache induced by food components and additives, and it was coded under ICHD-2's group 8 "Headache attributed to a substance or its withdrawal".⁴² This type of headache is usually throbbing and exacerbated by physical activity, develops within 12 hours after exposure, disappears within 72 hours after ingestion and occurs exclusively with the specific food component or additive. The following foods are frequently related as migraine

triggers: chocolate, cheese, milk and dairies, citrus, sausages, fatty and fried foods, condiments and alcohol.

Other known triggers are described. The prolonged visual effort can trigger headache in children who have refractive errors. Standing up, generally, may trigger headache attributed to low cerebrospinal fluid pressure. Mandibular movements or mastication can trigger headache attributed to temporomandibular disorder.

Headache Diary

The headache diary is a fundamental instrument in the follow-up of patients with headache. In the pediatric population, it has not only therapeutic implications, but also diagnostic ones. There are numerous types of headache diaries, some of them prioritize treatment-related aspects, while others, trigger factors. The diary presented herein (Figure 1) has been developed to the specific follow-up of children and adolescents with headache.

Figure 1. Headache diary
In a calendar format, the patient or her parents fulfill

Headache diary																																
	Month:															Year:																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Dawn (midnight-6am)																																
Morning (6-noon)																																
Afternoon (noon-6pm)																																
Night (6pm-midnight)																																
Unilateral																																
Bilateral																																
Pressure / squeeze																																
Throbbing / pulsating																																
Worsen with exercise																																
Nausea																																
Vomiting																																
Photophobia																																
Phonophobia																																
Aura																																
Medication																																
Response (++)/+/-																																
Menstruation																																
Trigger																																
HS =	Pain intensity: (1) mild, the child continues to play and jump; (2) moderate, the child stops eating and jumping, but doesn't lay down; (3) strong, the child lays down and might cry due to the pain Fill in according to the headache intensity Fill in with an X Fill in according to the treatment response (++)/+/ -																															



(1) mild



(2) moderate



(3) strong



the days and periods of the month in which the attacks occurred, as well as the intensity sorted in numbers according to a visual analog scale. At the end of the month or the stipulated period, the sum of pains indicates the headache score (HS), reflecting the intensity, frequency and duration of attacks, assisting the clinician to evaluate the treatment effectiveness. In the rows below of the diary, headache's characteristics are assessed, such as location, type of pain, if exacerbated by physical exercise, accompanying symptoms, aura, response to analgesics, menstrual period and other trigger factors. The last row is used to other relevant information, for instance, the presence of other recurrent signs and symptoms, such as childhood periodic syndromes.

The prospective observation of the headache attacks through a diary, in general, defines the diagnosis of a primary headache, elucidating doubts coming from lack or imprecise information reported by the child or her parents. Furthermore, it helps the clinician to assess the therapeutic strategy adopted. Nowadays, the sharing of digital headache diaries among patients, their parents and physicians contribute substantially to the follow-up.

General Approaches to Migraine Treatment

The first therapeutic measure is to provide migraine information to the caregivers and the patient himself, in the cases of adolescents. It is crucial to reassure that the cause of the headache is not a serious or life-threatening intracranial disorder. Usually, the fear of family members is of tumors or aneurysms. The following recommendations about healthy lifestyle habits should be made:

Sleep. Sleep and wake times should not vary too much. For patients with frequent attacks, in which changes in sleep habits are clear triggers, we recommend maintaining the sleep schedule also on weekends, holidays and even during school vacations. Moreover, the total nighttime sleep is very important and varies according to age group: on average, 10 hours during early childhood, 9 hours during middle and late childhood, and 8 hours during adolescence. In the latter, besides the reduction in total nocturnal sleep time, circadian rhythm disorders (mainly delayed sleep-wake phase disorder) have been observed more frequently, and should be addressed as well.

Food. Balanced and at regular intervals, avoiding prolonged periods of fasting. Green vegetables are rich in riboflavin, a vitamin that has been shown to be effective as a prophylactic supplement for the treatment of migraine.⁴³ There is no absolute indication to systematically restrict

any type of food, unless an unequivocal relationship is identified (i.e., through the headache diary). Overweight or obese patients should be oriented to lose weight, through a nutritionist and pediatrician joint follow-up. Caffeinated or cola-based drinks should be ingested with moderation. Diet products should be avoided. It is also important to maintain adequate hydration.

Regular physical activity. Recreational and ludic in early childhood. Sports in late childhood and adolescence.

Use of contraceptive. For female adolescents with frequent migraine attacks and in use of combined oral contraceptives (estrogen and progestin), even at a low dose, the change for a progestin-only contraceptive should be considered.⁴⁴

Substance use. In adolescents, the possibility of the headache being associated with alcohol, tobacco and illicit drugs should be kept in mind, and their use should be discontinued.

Medication-overuse. Although not yet well established in the pediatric population, acute medication-overuse is considered as the use of analgesics, non-steroidal anti-inflammatory drugs, opioids, triptans and ergotamine derivatives for 15 (10 for triptans) or more days per month for at least 3 consecutive months. In such cases, acute medications should be discontinued, and prophylactic treatment introduced, if indicated.

Acute Treatment

Migraine acute treatment aims not only to the relief of headache, but also the accompanying symptoms and burden associated, allowing the child to return to usual functioning and preventing the attack recurrence in a short period of time. The treatment should be based in the following general principles: a) use medications in adequate doses; b) start as soon as possible, as soon as the attack starts (i.e., for patients who present aura, medication should be administered before pain onset); c) avoid overuse of acute medications.

For many children, sleeping is effective in the relief of headache. The younger the patient is, the more effective it tends to be. Accordingly, resting in a dark, quiet and well-ventilated space during the attack is indicated in all cases.

Table 1 presents the medications available in Brazil used for acute treatment of migraine in children and adolescents.



Table 1. Drugs used to treat migraine attacks in children and adolescents, available in Brazil. Dosage, dosage forms and scientific evidence*

Drug Age**	Dosage		Dosage forms	Side effects	Recommendations*
	< 40 kg	> 40 kg			
Ibuprofen > 4 yrs	10 mg/kg	400 – 1,200 mg/dose; Up to 1.6 g/day	OS 100 mg/ml (10 mg/drop) Tb 200; 300; 400; 600 mg	Dizziness, headache, dyspepsia, nausea, vomiting, diarrhea, abdominal pain, flatulence, blood dyscrasias	Class I Level A
Acetaminophen > 4 yrs	15 mg/kg/dose	500 – 1,000 mg/dose; up to 4 g/day	OS 200 mg/ml (13,3 mg/drop) Tb 500; 750 mg	Nausea, vomiting, urticaria and liver toxicity (rare)	Class I Level B
Metamizol dypirone > 4 yrs	10 mg/kg	500 – 1,000 mg/dose; up to 3 g/day	OS 500 mg/ml (25 mg/drop) Tb 500 mg; 1,000 mg IS 500 mg	Hypotension, urticaria and other anaphylactic reactions, blood dyscrasias, acute kidney failure (rare)	Class IV Level U
Ketorolac > 4 yrs	0.5 - 1 mg/kg, SL, single dose; up to 20 mg/dose		Tb SL 10 mg	Diarrhea, headache, nausea, dizziness, drowsiness, oedema, dyspepsia, arterial hypertension, urticaria, purpura	Class IV Level U
Piroxicam > 12 yrs	0.25 – 0.5 mg/kg, SL, single dose; up to 20 mg/dose		Tb SL 20 mg	Oral ulcers, diarrhea, constipation, flatulence, headache, nausea, dizziness, drowsiness, oedema, abdominal pain, arterial hypertension, urticaria, purpura	Class IV Level U
Sumatriptan > 8 yrs	10 - 20 mg/dose		Nasal spray 10 mg/0,1 ml (10 mg per dose)	Taste alteration, paresthesia, facial flush, chest discomfort, fatigue	Class I Level A
Rizatriptan > 6 yrs	5 mg	10 mg	Tb 5mg; 10 mg RDT 10 mg	Asthenia, dizziness, dry mouth	Class I Level B
Zolmitriptan > 12 yrs		2.5 - 5 mg	Tb 2.5 mg RDT 2,5 mg	Dizziness, drowsiness, weakness	Class IV Level U
Sumatriptan + Naproxen	Only for adolescents 50 mg Sumatriptan + 500 mg Naproxen		Tb 50/500 mg Tb 85/500 mg	Dizziness, drowsiness, paresthesia; nausea, dyspepsia, dry mouth; chest pain / discomfort, neck pain / discomfort, asthenia, heat sensation, muscular stiffness, palpitation	Class I Level A
Chlorpromazine > 12 yrs		0.1 mg/kg, IV, up to 25 mg/dose	IS 25 mg	Drowsiness, hypotension, xerostomia, constipation, urinary retention, QT interval extension, extrapyramidal motor changes, neuroleptic malignant syndrome (rare)	Class IV Level U
Ondansetron§ (if nausea and vomiting) > 2 yrs	4 mg SL 0,1 mg/kg, IV	8 - 16 mg SL 4 mg, IV	Tb SL 4 e 8 mg IS 4 e 8 mg	Headache, Drowsiness, fatigue, extrapyramidal motor changes (rare)	Class IV Level U
Metoclopramide (if nausea and vomiting)	children <6 yrs (IV/oral): 0.1-0.2 mg/kg, 3-4 x/day, up to 10 mg per dose	children > 6 yrs (IV/oral): 0,5-1 mg/kg, 3-4 x/day, up to 10mg per dose	Tb 10 mg OS (syrup) 1 mg/ml OS (drops) 4mg/ml IS 5mg/ml	Drowsiness, extrapyramidal motor changes, diarrhea, asthenia, hypotension, bradycardia, liquid retention and allergic reactions	Class IV Level U

Tb: tablet; OS: oral suspension; IS: injectable solution; SL: sublingual; IV: intravenous; RDT: rapidly disintegrating tablet; * For class definitions and evidence levels, see the American Academy of Neurology recommendations; ** According to studies demonstrating efficacy and safety; § Repeat every 8 hours, until there is complete headache improvement (maximum of 20 doses).



Based on the literature and in our experience, we present an algorithm for the management of migraine attacks in the pediatric population (Figure 2).

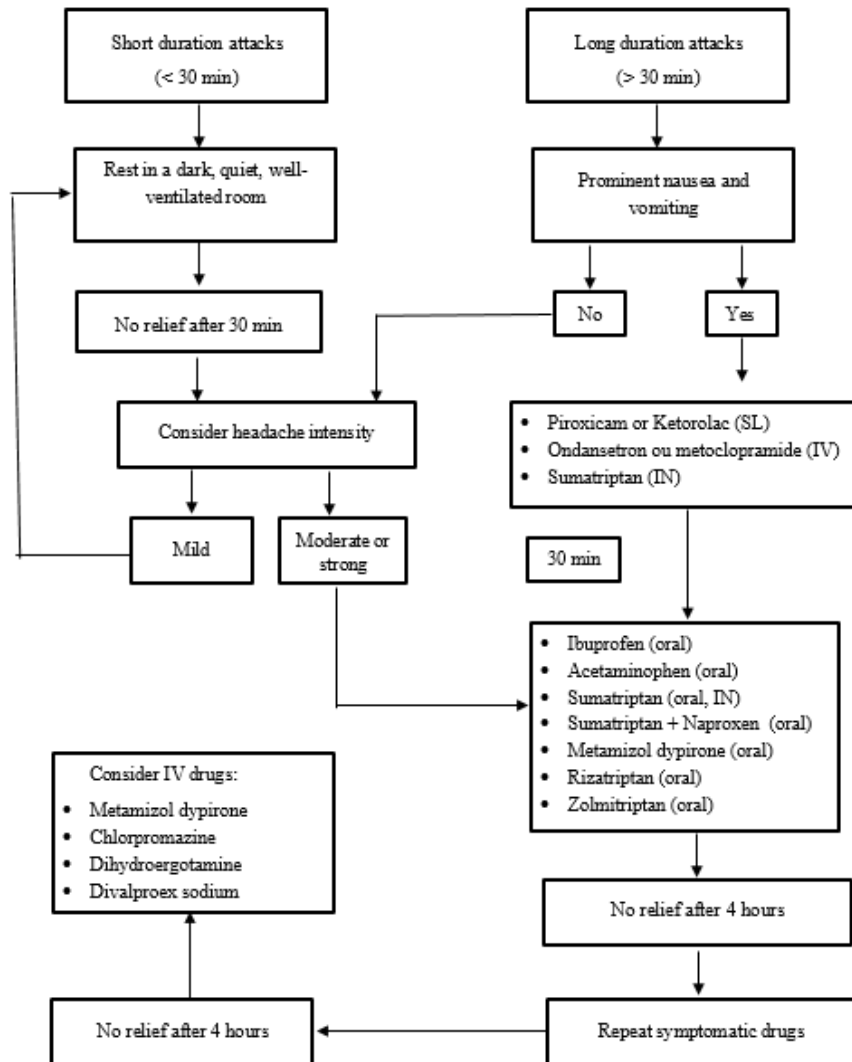


Figure 2. Algorithm for Acute Treatment of Migraine

The clinician should be aware of possible adverse effects, mainly those most frequently reported, and contraindications. Absolute contraindications to the use of triptans include: history of cardiovascular disease, stroke, transient ischemic attack, myocardial infarction, peripheral or visceral vascular disease, coronary vasospasm (such as Prinzmetal's Angina), and cardiac conduction disorders (i.e., Wolff-Parkinson-White Syndrome). Scientific evidence indicate safety of triptans in the aura phase. However, in patients with recent onset of auras or complex auras, such use should be avoided until the possibility of stroke is ruled out.⁴⁴

The use of ergotamine derivatives and opioids in this age group should be avoided, given the lack of sufficient evidence of efficacy and safety, as well as the potential risk of adverse effects and medication-overuse.

Preventive Treatment

The preventive (or prophylactic) treatment of migraine aims to reduce the frequency, duration and intensity of attacks, increase the response to acute medications, and improve the patient's quality of life. Therefore, it should be considered



for individuals with frequent attacks (more than one attack per week), or for those with very disabling attacks.

The clinician must always keep in mind the perspective of the functional impact of the disease. For example, a child who has four attacks per month, but does not miss any school day, and does not have her school performance impaired might not need preventive treatment. On the contrary, a child with an average of two attacks per month, with plenty of vomiting and school absenteeism, may need it. The decision should always be shared with the family.

In order to assess the success or failure of therapy, prophylactic medication should be used for a minimum period of 6 weeks. We aim for no more than two attacks of mild or moderate intensity per month, and that respond well to symptomatic medication. Consequently, our approach is to discontinue preventive medication after a period of at least 6 months of satisfactory control of the attacks. Table 2 presents the medications that can be used for the preventive treatment of migraine.

Table 2. Drugs used for the preventive treatment of migraine attacks in children and adolescents, available in Brazil. Dosage, dosage forms and scientific evidence*

Drug*	Dosage	Dosage forms	Side effects	Recommendations**
Amitriptyline	0.25 – 1 mg/kg/day, 24/24 h (10 – 75 mg/day)	Tb 10, 25, 75 mg	Drowsiness, appetite gain, weight gain	Class IV Level U
Trazodone	1 mg/kg/day, 24/24 h (25 mg – 50 mg/day)	Tb 50, 100 mg Tb retard 150 mg	Suicidal thoughts, increase in depressive symptoms	Class II Level U
Divalproex sodium	15 – 45 mg/kg/day, 12/12 h (250 mg – 1,000 mg/day)	Tb 250, 500 mg Tb ER 250, 500 mg Tb sprinkles 125 mg	Gastrointestinal discomfort, weight gain, drowsiness, dizziness, tremor	Class IV Level U
Topiramate	3 – 9 mg/kg/day, 12/12 h (25 – 200 mg/day)	Tb 25, 50, 100 mg Tb sprinkles 15, 25 mg	Appetite decrease, weight loss, drowsiness, fatigue, dizziness, hypohidrosis, bradypsychism (less frequent then in adults), paresthesia, visual clouding	Class IV Level U
Levetiracetam	20 – 40 mg/kg/day, 12/12 h (250 – 500 mg/day)	Tb 250, 500, 750, 1,000 mg OS 100 mg/ml	Drowsiness, dizziness and irritability	Class IV Level U
Gabapentin	15 mg/kg/day, 12/12 h or 8/8 h (300 – 900 mg/day)	Tb 300, 400, 600 mg	Not described	Class IV Level U
Propranolol	1 – 4 mg/kg/day, 12/12 h or 8/8 h (20 – 120 mg/day)	Tb 10, 40, 80 mg Tb LA 80 mg	Nausea, abdominal pain and insomnia	Class II Level U
Flunarizine	5 – 10 mg/day, 24/24 h	Tb 10 mg Drops: 20 drops = 5 mg	Weight gain, fatigue, gastrointestinal discomfort	Class I Level B
Cyproheptadine §	0.25 – 1.5 mg/kg/day, 24/24 h (2 – 8 mg/day)	Tb 4 mg OS 1 mg/ml, 2 mg/5 ml, 4 mg/5 ml	Drowsiness, appetite increase, weight gain	Class IV Level U
Botulinum toxin A	100 U	Vials 100 U, 200 U	Palpebral ptosis, visual clouding, bruising at injection sites	Class IV Level U

Tb: tablet; OS: oral suspension

* For class definitions and evidence levels, see the American Academy of neurology recommendations.

** According to studies demonstrating efficacy and safety.

§ Night use, about 1 hour before expected sleeping time.



Randomized controlled studies for migraine prophylaxis in children and adolescents are still scarce. However, the effectiveness of preventive medications appears to be similar in adults and children. The drug choice is generally based on the following factors: 1) presence of contraindications (i.e., beta-blockers for children with asthma); 2) drug profile that may additionally treat comorbid conditions (Figure 3).

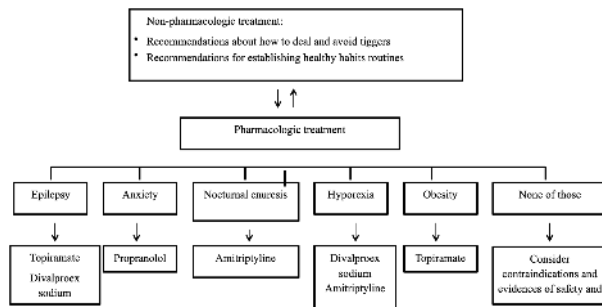


Figure 3. Algorithm for preventive treatment of migraine

CGRP-targeted Treatments

Currently, migraine treatment is under a new and important transition period represented by the advent of treatments targeting the calcitonin gene-related peptide (CGRP) pathway.

It is rising the number of monoclonal antibodies approved for children and adolescents for the treatment of neoplasms, auto-immune diseases, prevention of the respiratory syncytial virus infection, transplants' rejection, chronic arthritis, Crohn's disease, psoriasis, asthma and allergic rhinitis, and refractory atopic dermatitis.⁴⁵ Nonetheless, at the present time, the literature has only one published open-label study with adolescents with chronic daily headache.⁴⁶ More clinical studies assessing anti-CGRP drugs in children and adolescents with migraine are on the way.

Non-pharmacologic Treatment

Behavioral Interventions

Besides the importance of measures that stimulate a better lifestyle in children and adolescents with migraine, structured behavioral interventions present positive evidence of effectiveness and safety when compared to placebo, and even to medications routinely used in this condition. Such interventions include relaxation techniques, biofeedback, coping strategies, multimodal treatment, cognitive behavioral therapy (CBT), and other.

CBT consists in aware the patient about the wide interaction among thoughts, emotions, somatic responses and

behavior, teaching the child or the adolescent strategies of positive and realistic (acceptance and auto-sufficiency) thinking, eliminating the interference of dysfunctional thoughts without reality basis (catastrophizing, fear, anxiety) with regards to headache attacks.⁴⁷

Biofeedback's core strategy is to train the patient to modulate her somatic responses to stress, developing her attention and corporal consciousness, easing her autoregulation of physiologic responses.

Both interventions have evidence of reduction in the frequency, intensity and duration of migraine attacks provided by placebo- and other drugs-controlled studies, such as amitriptyline.^{48, 49}

Nutraceuticals

Despite the high expectations of supplements' success in the treatment of pediatric migraine, the positive evidence derives only from open-label trials, while the controlled ones could not demonstrate unequivocal superiority against placebo. Accordingly, some studies are found in the literature regarding riboflavin^{50, 51}, coenzyme Q10⁵², magnesium⁵³, melatonin⁵⁴, butterbur^{55, 56} and vitamin-D.⁵⁷

Conclusions

Whoever is treating migraine in children and adolescents should regard that "no evidence of efficacy is not evidence of no efficacy".⁵⁸ Many of the migraine preventive medications utilized in these ages are prescribed routinely and as off-label strategies, however, these treatments show safety and efficacy, at least from a clinical perspective. Are they really effective or are the practitioners only observing the placebo effect? Another important question that arises: does it matter? Even though placebo is considered an enemy of clinical trials, it is, probably, a great friend of the perspicacious clinicians. This is not an argument in favor of ignoring the evidence, instead it is an acknowledgement that practitioners should use at its best the limited amount of available evidence, especially in circumstances as migraine preventive treatment.

Secondarily, the advances in clinical trials' design have not followed the significant advances observed in migraine diagnosis, epidemiology and burden in childhood and adolescence. This mismatch becomes more frustrating when considering recent evidence indicating the burden in the children's and their families' quality of life, mental health, school's attendance, and academic performance. Therefore, the lack of evidence must not be translated



into paralysis, with doctors ignoring children's suffering passively.

What should be done? 1) Bear in mind the burden of migraine in children and adolescents; 2) Whenever is possible, give preference to the medications with the best available evidence of effectiveness, tolerability and safety; 3) Whenever no evidence is available, or when first-line therapies have failed, choose a medication according to its plausibility, proven effectiveness in adults trials, and proven safety of the medication in children.

Lack of evidence associated with lack of reasoning to navigate in this context is an undesirable combination in the treatment of migraine in childhood and adolescence.

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Author's Contributions

MAA, RA have both contributed to the conception, acquisition, analysis, and interpretation of the data, edited and revised the manuscript

Marco Antônio Arruda

<https://orcid.org/0000-0001-8064-2094>

Renato Arruda

<https://orcid.org/0000-0002-2350-2594>

References

- James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, . . . Murray CJL. **Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.** *The Lancet* 2018;392(10159):1789-1858 Doi: 10.1016/s0140-6736(18)32279-7
- Leonardi M, Grazi L, D'Amico D, Martelletti P, Guastafierro E, Toppo C and Raggi A. **Global Burden of Headache Disorders in Children and Adolescents 2007–2017.** *International Journal of Environmental Research and Public Health* 2020;18(1):Doi: 10.3390/ijerph18010250
- Arruda MA, Guidetti V, Galli F, Albuquerque RCAP and Bigal ME. **Childhood Periodic Syndromes: A Population-Based Study.** *Pediatric Neurology* 2010;43(6):420-424 Doi: 10.1016/j.pediatrneurol.2010.06.016
- Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.** *Cephalalgia* 2018;38(1):1-211 Doi: 10.1177/0333102417738202
- Rossi R, Versace A, Lauria B, Grasso G, Castagno E, Ricceri F, . . . Urbino AF. **Headache in the pediatric emergency department: A 5-year retrospective study.** *Cephalalgia* 2017;38(11):1765-1772 Doi: 10.1177/0333102417748907
- Patterson-Gentile C and Szperka CL. **The Changing Landscape of Pediatric Migraine Therapy.** *JAMA Neurology* 2018;75(7):Doi: 10.1001/jamaneurol.2018.0046
- Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society.** *Cephalalgia* 1988;8 Suppl 7(1-96)
- Olesen J. **The International Classification of Headache Disorders, 2nd edition: application to practice.** *Funct Neurol* 2005;20(2):61-68
- Machado LR. **Cefaléias na infância e adolescência.** *Arquivos de Neuro-Psiquiatria* 2008;66(2a):291-291 Doi: 10.1590/s0004-282x2008000200039
- Abu-Arafeh I, Razak S, Sivaraman B and Graham C. **Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies.** *Developmental Medicine & Child Neurology* 2010;52(12):1088-1097 Doi: 10.1111/j.1469-8749.2010.03793.x
- Arruda MA and Bigal ME. **Behavioral and emotional symptoms and primary headaches in children: A population-based study.** *Cephalalgia* 2012;32(15):1093-1100 Doi: 10.1177/0333102412454226
- Arruda MA, Guidetti V, Galli F, Albuquerque RCAP and Bigal ME. **Primary headaches in childhood – A population-based study.** *Cephalalgia* 2010;30(9):1056-1064 Doi: 10.1177/0333102409361214
- Wöber-Bingöl Ç. **Epidemiology of Migraine and Headache in Children and Adolescents.** *Current Pain and Headache Reports* 2013;17(6):Doi: 10.1007/s11916-013-0341-z
- Arruda MA, Bordini CA, Ciciarelli MC and Speciali JG. **Decreasing the minimal duration of the attack to 1 hour: is this sufficient to increase the sensitivity of the ICHD-II diagnostic criteria for migraine in childhood?** *The Journal of Headache and Pain* 2004;5(2):131-



- 136 Doi: 10.1007/s10194-004-0081-x
15. Barea LM, Tannhauser M and Rotta NT. **An Epidemiologic Study of Headache Among Children and Adolescents of Southern Brazil.** *Cephalalgia* 2016;16(8):545-549 Doi: 10.1046/j.1468-2982.1996.1608545.x
 16. Albuquerque RP, Santos AB, Tognola WA and Arruda MA. **An epidemiologic study of headaches in brazilian schoolchildren with a focus on pain frequency.** *Arquivos de Neuro-Psiquiatria* 2009;67(3b):798-803 Doi: 10.1590/s0004-282x2009000500003
 17. Arruda MA, Albuquerque RCAP and Bigal ME. **Uncommon Headache Syndromes in the Pediatric Population.** *Current Pain and Headache Reports* 2011;15(4):280-288 Doi: 10.1007/s11916-011-0192-4
 18. Arruda MA, Bonamico L, Stella C, Bordini CA and Bigal ME. **Cluster headache in children and adolescents: Ten years of follow-up in three pediatric cases.** *Cephalalgia* 2011;31(13):1409-1414 Doi: 10.1177/0333102411418015
 19. Wilne SH. **The presenting features of brain tumours: a review of 200 cases.** *Archives of Disease in Childhood* 2006;91(6):502-506 Doi: 10.1136/adc.2005.090266
 20. Burton LJ, Quinn B, Pratt-Cheney JL and Pourani M. **Headache etiology in a pediatric emergency department.** *Pediatric Emergency Care* 1997;13(1):1-4 Doi: 10.1097/00006565-199702000-00001
 21. Lewis DW and Qureshi F. **Acute Headache in Children and Adolescents Presenting to the Emergency Department.** *Headache: The Journal of Head and Face Pain* 2000;40(3):200-203 Doi: 10.1046/j.1526-4610.2000.00029.x
 22. Akinci A, Güven A, Degerliyurt A, Kibar E, Mutlu M and Citirik M. **The correlation between headache and refractive errors.** *Journal of American Association for Pediatric Ophthalmology and Strabismus* 2008;12(3):290-293 Doi: 10.1016/j.jaapos.2007.11.018
 23. **The International Classification of Headache Disorders, 3rd edition (beta version).** *Cephalalgia* 2013;33(9):629-808 Doi: 10.1177/0333102413485658
 24. Aaseth K, Grande RB, Kværner K, Lundqvist C and Russell MB. **Chronic rhinosinusitis gives a ninefold increased risk of chronic headache. The Akershus study of chronic headache.** *Cephalalgia* 2009;30(2):152-160 Doi: 10.1111/j.1468-2982.2009.01877.x
 25. Arita JH, Lin J, Pinho RS, Minett TSC, de Souza Vitalle MS, Fisberg M, . . . Masruha MR. **Adolescents with chronic migraine commonly exhibit depressive symptoms.** *Acta Neurologica Belgica* 2012;113(1):61-65 Doi: 10.1007/s13760-012-0135-9
 26. Masruha MR, Lin J, Minett TSC, Vitalle MSS, Fisberg M, Vilanova LCP and Peres MFP. **Social anxiety score is high in adolescents with chronic migraine.** *Pediatrics International* 2012;54(3):393-396 Doi: 10.1111/j.1442-200X.2011.03555.x
 27. Paschoal JKSF, Lin J, Pinho RS, Andreoni S, Minett TSC, Vitalle MSS, . . . Masruha MR. **Psychiatric symptoms may contribute to poor quality of life in adolescents with migraine.** *Pediatrics International* 2013;55(6):741-747 Doi: 10.1111/ped.12178
 28. Arruda MA, Arruda R, Guidetti V and Bigal ME. **Psychosocial Adjustment of Children With Migraine and Tension-Type Headache - A Nationwide Study.** *Headache: The Journal of Head and Face Pain* 2015;55(39-50) Doi: 10.1111/head.12510
 29. Arruda MA, Guidetti V, Galli F, Albuquerque RCAP and Bigal ME. **Frequent headaches in the preadolescent pediatric population.** *Neurology* 2010;74(11):903-908 Doi: 10.1212/WNL.0b013e3181d561a2
 30. Gorodzinsky AY, Hainsworth KR and Weisman SJ. **School Functioning and Chronic Pain: A Review of Methods and Measures.** *Journal of Pediatric Psychology* 2011;36(9):991-1002 Doi: 10.1093/jpepsy/jsr038
 31. Arruda MA and Bigal ME. **Migraine and migraine subtypes in preadolescent children: Association with school performance.** *Neurology* 2012;79(18):1881-1888 Doi: 10.1212/WNL.0b013e318271f812
 32. Wöber-Bingöl Ç, Wöber C, Uluduz D, Uygunoğlu U, Aslan TS, Kernmayer M, . . . Steiner TJ. **The global burden of headache in children and adolescents – developing a questionnaire and methodology for a global study.** *The Journal of Headache and Pain* 2014;15(1):Doi: 10.1186/1129-2377-15-86
 33. Rocha-Filho PAS and Santos PV. **Headaches, Quality of Life, and Academic Performance in Schoolchildren and Adolescents.** *Headache: The Journal of Head and Face Pain* 2014;54(7):1194-1202 Doi: 10.1111/head.12394
 34. Bellini B, Arruda M, Cescut A, Saulle C, Persico A, Carotenuto M, . . . Guidetti V. **Headache and comorbidity in children and adolescents.** *The Journal of Headache and Pain* 2013;14(1):Doi: 10.1186/1129-2377-14-79
 35. Guidetti V, Alberton S, Galli F, Mittica P and Salvi E. **Gender, migraine and affective disorders in the course of the life cycle.** *Functional Neurology* 2009;24(29-40)
 36. Galli F, Canzano L, Scalisi TG and Guidetti V. **Psychiatric disorders and headache familial**



- recurrence: a study on 200 children and their parents.** *The Journal of Headache and Pain* 2009;10(3):187-197 Doi: 10.1007/s10194-009-0105-7
37. Varni JW, Limbers CA and Burwinkle TM. **Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL™ 4.0 Generic Core Scales.** *Health and Quality of Life Outcomes* 2007;5(1):Doi: 10.1186/1477-7525-5-43
 38. Guidetti V, Galli F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O and Trillo S. **Headache and psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study.** *Cephalalgia* 1998;18(7):455-462 Doi: 10.1046/j.1468-2982.1998.1807455.x
 39. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, . . . Guidetti V. **Headache and Recurrent Abdominal Pain: A Controlled Study by the Means Of The Child Behaviour Checklist (CBCL).** *Cephalalgia* 2016;27(3):211-219 Doi: 10.1111/j.1468-2982.2006.01271.x
 40. Anttila P, Sourander A, Metsähonkala L, Aromaa M, Helenius H and Sillanpää M. **Psychiatric Symptoms in Children With Primary Headache.** *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(4):412-419 Doi: 10.1097/00004583-200404000-00007
 41. Virtanen R, Aromaa M, Koskenvuo M, Sillanpää M, Pulkkinen L, Metsähonkala L, . . . Kaprio J. **Externalizing Problem Behaviors and Headache: A Follow-up Study of Adolescent Finnish Twins.** *Pediatrics* 2004;114(4):981-987 Doi: 10.1542/peds.2003-1103-L
 42. Olesen J. **Preface to the Second Edition.** *Cephalalgia* 2016;24(1_suppl):9-10 Doi: 10.1111/j.1468-2982.2003.00824.x
 43. Lateef T, He J-P, Nelson K, Calkins ME, Gur R, Gur R and Merikangas KR. **Physical-Mental Comorbidity of Pediatric Migraine in the Philadelphia Neurodevelopmental Cohort.** *The Journal of Pediatrics* 2019;205(210-217) Doi: 10.1016/j.jpeds.2018.09.033
 44. Goodman R. **Psychometric Properties of the Strengths and Difficulties Questionnaire.** *Journal of the American Academy of Child & Adolescent Psychiatry* 2001;40(11):1337-1345 Doi: 10.1097/00004583-200111000-00015
 45. Barkley RA. **Executive functions: What they are, how they work, and why they evolved.** The Guilford Press; 2012 p.
 46. S. G and JA N. **Handbook of Executive Functioning** ed Editor ^ editor New York: NY: Springer-Verlag; 2014 p.
 47. White LK, Moore TM, Calkins ME, Wolf DH, Satterthwaite TD, Leibenluft E, . . . Gur RE. **An Evaluation of the Specificity of Executive Function Impairment in Developmental Psychopathology.** *Journal of the American Academy of Child & Adolescent Psychiatry* 2017;56(11):975-982.e973 Doi: 10.1016/j.jaac.2017.08.016
 48. Shanmugan S, Wolf DH, Calkins ME, Moore TM, Ruparel K, Hopson RD, . . . Satterthwaite TD. **Common and Dissociable Mechanisms of Executive System Dysfunction Across Psychiatric Disorders in Youth.** *American Journal of Psychiatry* 2016;173(5):517-526 Doi: 10.1176/appi.ajp.2015.15060725
 49. Martel MM, Pan PM, Hoffmann MS, Gadelha A, do Rosário MC, Mari JJ, . . . Salum GA. **A general psychopathology factor (P factor) in children: Structural model analysis and external validation through familial risk and child global executive function.** *Journal of Abnormal Psychology* 2017;126(1):137-148 Doi: 10.1037/abn0000205
 50. Neumann A, Muetzel RL, Lahey BB, Bakermans-Kranenburg MJ, van Ijzendoorn MH, Jaddoe VW, . . . Tiemeier H. **White Matter Microstructure and the General Psychopathology Factor in Children.** *Journal of the American Academy of Child & Adolescent Psychiatry* 2020;59(11):1285-1296 Doi: 10.1016/j.jaac.2019.12.006
 51. Cantin RH, Gnaedinger EK, Gallaway KC, Hesson-McInnis MS and Hund AM. **Executive functioning predicts reading, mathematics, and theory of mind during the elementary years.** *Journal of Experimental Child Psychology* 2016;146(66-78) Doi: 10.1016/j.jecp.2016.01.014
 52. Jacobson LA, Koriakin T, Lipkin P, Boada R, Frijters JC, Lovett MW, . . . Mahone EM. **Executive Functions Contribute Uniquely to Reading Competence in Minority Youth.** *Journal of Learning Disabilities* 2016;50(4):422-433 Doi: 10.1177/0022219415618501
 53. Oberer N, Gashaj V and Roebbers CM. **Executive functions, visual-motor coordination, physical fitness and academic achievement: Longitudinal relations in typically developing children.** *Human Movement Science* 2018;58(69-79) Doi: 10.1016/j.humov.2018.01.003
 54. Arruda MA, Arruda R and Anunciação L. **Psychometric properties and clinical utility of the executive function inventory for children and adolescents: a large multistage populational study including children with ADHD.** *Applied Neuropsychology: Child* 2020;11(1):1-17 Doi: 10.1080/21622965.2020.1726353
 55. Arruda R., Anunciacao L. and Arruda M. **Executive**



- Function in Adolescents with Chronic Headache: A Population Study.** *Neurology* 2020
56. Costa-Silva MA, Prado ACA, Souza LC, Gomez RS and Teixeira AL. **Cognitive functioning in adolescents with migraine.** *Dementia & Neuropsychologia* 2016;10(1):47-51 Doi: 10.1590/s1980-57642016dn10100009
57. Arruda M, Speciali J, Ciciarelli M and Bordini C. **Childhood Migraine: Diagnostic Problems.** *Cephalalgia* 1995;15(16_suppl)(82-82)
58. Arruda MA. **No Evidence of Efficacy or Evidence of No Efficacy.** *JAMA Pediatrics* 2013;167(3):Doi: 10.1001/jamapediatrics.2013.1105