Invited paper

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Chronic Migraine in the Pediatric Population – Lessons Learned

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In predisposed individuals, migraine evolves into a stage of daily or nearly daily headaches, known as chronic migraine. Although relatively prevalent and debilitating at all ages, chronic migraine is particularly aggressive in the pediatric population. Several risk factors for chronic migraine have been identified, largely due to two very large longitudinal studies, the American Migraine Prevalence and Prevention Study (AMPP) and the Attention Brazil Project (ABP). This review summarizes lessons learned from these studies that included children from 5 to 19 years of age. We start by contextualizing chronic migraine and by offering a systematic approach to diagnosis. We then discuss pre-natal and post-natal risk factors for migraine transformation, and close by reviewing treatment strategies, ultimately attempting to offer a meaningful overview of chronic migraine in pre-adults based on our experience conducting these studies.

Keywords: chronic migraine, pediatric migraines, American Migraine Prevalence and Prevention study, Attention Brazil Project, risk factors, medication overuse headaches, neurology

INTRODUCTION

Until relatively recent times, migraine was considered to occur only episodically, on less than 15 days per month. As recently as the 90s, the International Classification of Headache Disorders (ICHD-1) did not contemplate the diagnosis of chronic migraine (CM) (1), and individuals with daily or nearly daily headaches were diagnosed as suffering from multiple headache disorders (2).

It was clear, however, that in some individuals, episodic migraine progressed to a condition initially termed transformed migraine (3). This condition is now known as CM due to ultimate acceptance that migraine can indeed occur daily or nearly daily (4) .

One of the authors (MEB) was very involved in the discussion that shaped the understanding of CM, being the co-chair of the classification committee of the International Headache Society and dedicating the bulk of his career to researching the factors associated with the progression from episodic migraine to CM, with a special emphasis on the role of acute migraine treatment in migraine progression. One of us (MAA) also led the largest and most comprehensive study describing migraine and frequent migraines in the pediatric population. This review is an attempt to summarize lessons learned in this process, focusing primarily on our original studies. For the purpose of this review, we will focus on lessons primarily generated by the American Migraine Prevalence and Prevention (AMPP) and on the Attention Brazil Project (ABP) studies.

The AMPP is the largest conducted migraine cohort to date (5-8). In 2004, validated questionnaires were mailed to a representative sample of 120,000 households in the U.S. The questionnaires contained questions about headache occurrence, symptoms, medication use, and missed time from work because of headache along with many other questions. Surveys were returned by 77,879 households, which included 162,756 household members aged 12 years and older. After mapping the prevalence of headaches in the U.S. by demographics, a sample of 24,000 participants with headaches were longitudinally resurveyed on a yearly basis for 7 years. The primary aim of the study was to identify

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predictors of outcomes (remission, stability, and progression).

The ABP was a large population study aiming to investigate mental health and development of preadolescent children in Brazil. The project consisted of 2 phases. In Phase 1, the target sample population included all children aged 5 to 12 years registered in the public school system of a city demographically representative of the Brazilian population. Over 2,000 children participated in the study. Mothers were directly interviewed using standardized and validated questionnaires, and detailed information was obtained on overall health, learning conditions (eg, attention deficit hyperactivity disorder [ADHD]), socioeconomic conditions, parental overall health, particular exposures during pregnancy, and others. Headaches were assessed according to the ICHD-2. Direct interviews were also conducted with teachers, as per the DSM-IV, in order to investigate impact of disorders, with a specific emphasis on understanding the impacts of migraines on learning. The second phase of the ABP was national and used the questionnaires validated in the first stage of the study (9-11). While the AMPP focused on the adolescent population, the ABP focused on the pre-adolescent population. Together they offer a meaningful and complementary map of migraine in pre-adults.

EPISODIC AND CHRONIC MIGRAINE IN THE PEDIATRIC POPULATION

As part of the AMPP Study, we found that the 1-year prevalence for episodic migraine in those from 12-17 years of age was 6.3% (12). The prevalence in boys was 5.0%; in girls it was 7.7%. Figure 1 displays the adjusted prevalence ratios (PRs), stratifying by sex including those up to 19 years of age. Two important lessons emerged (12): First, although the prevalence in adolescents is lower than what is seen in adults (12% overall), migraine is still very prevalent in adolescents. Second, the gender effect is little pronounced in pre-menstrual girls, becoming more evident in older ages, approaching the ratio in adults (3 women to 1 men) (Figure 1b).

To study the prevalence of frequent headaches in the younger pediatric population, we took advantage of the ABP. Overall, the prevalence of episodic migraine with or without aura was 3.9% in boys and 3.6% in girls, highlighting once more that the female predominance in migraine is only evident after puberty. Prevalence increased with age. Using the age of 6 as the reference (2.6%), prevalence was numerically increased in all subsequent ages, and significantly increased at the age of 10 or older (5.5%, RR = 2.13, 95% CI = 1.02-4.44) (Table 1) (11, 13).

Before we discuss the prevalence of CM, we find that a distinction is important. We have defended that the separation of episodic and chronic migraine by frequency (less than 15 days of headache and at least 15 days of

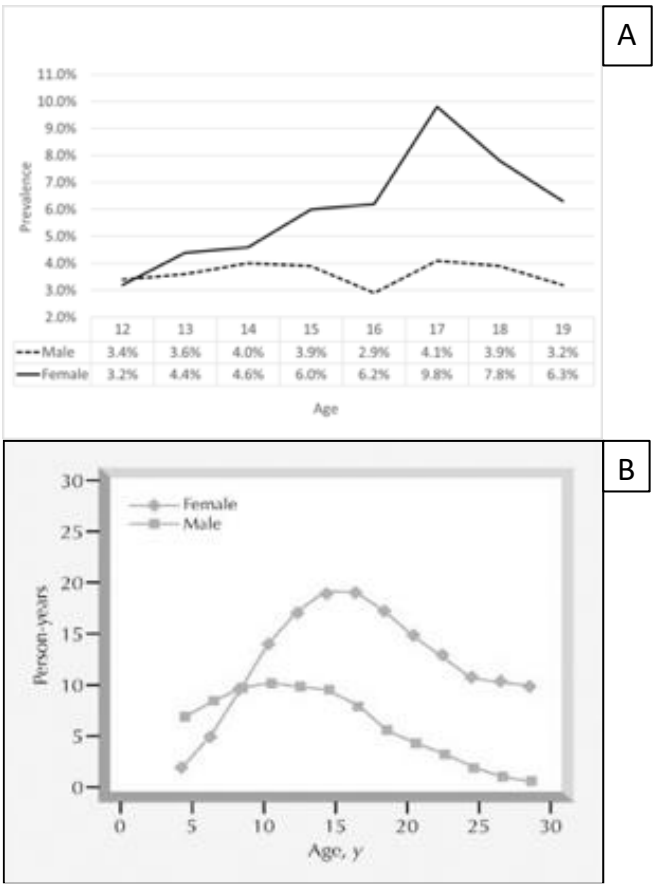

Figure 1- (a, based on (12)) Adjusted prevalence of migraine (episodic and chronic) by age and sex in the late pediatric and adolescent population; (b, based on (8)) Prevalence in adults

Table 1- Prevalence of migraine episodic and chronic migraine in pre-adolescent children (based on (11)).

	EPISODIC MIGRAINE		
AGE	**Overall**	**Girls**	**Boys**
< 6	2.58%	2.22%	2.92%
7	2.86%	3.53%	2.22%
8	3.25%	3.43%	3.11%
9	4.92%	3.16%	6.81%
10+	5.50%	3.07%	4.40%
OVERALL	3.76%	3.56%	3.95%
	Chronic Migraine		
AGE	**Overall**	**Age**	**Overall**
< 6	0.65%	0.89%	0.42%
7	1.14%	0.59%	1.67%
8	0.50%	1.14%	-
9	0.41%	0.40%	0.43%
10+	1.72%	3.79%	-
OVERALL	0.80%	1.15%	0.48%

headache, respectively) does not reflect its biology (14, 15). Indeed, when migraine increases in frequency to around 8-10 headaches per month, the pathophysiology, clinical features, and response to therapy becomes nearly indistinguishable than those with 15 or more days (the typical chronic migraineurs). We believe that the distinction should be among migraineurs with low/intermediate frequency of headaches, and high frequency/chronic migraines, which should be further subdivided in unremitting/refractory (virtually no pain-free periods) and remitting/responsive.

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In the ABP we also used the framework above. We found that the prevalence of high frequency episodic migraines was 2.52% overall, being 2.8% in girls and 2.3% in boys.

The prevalence of chronic migraine was 0.8% in this pre-adolescent population, being slightly more frequent in girls (1.15%) than in boys (0.48%) (Table 2). Therefore, two lessons emerge. First, although the prevalence of episodic migraine is higher in pre-adolescent boys than in girls, the latter group transforms to high frequency and chronic migraine at a much higher rate, being at increased risk of developing these outcomes. Second, the prevalence of very frequent headaches (10 or more per months) is a staggering 3.32% (13), making frequent migraines in the pediatric population one of the most prevalent neurological conditions in the pediatric population.

Table 2- 'Red flags' in the diagnosis of headache in children and adolescents (from our original work at (16)).

'Red Flags'	Consider	Possible investigation(s)
Sudden-onset	Subarachnoid hemorrhage, bleed into a mass, AVM, or aneurysm	Neuroimaging and lumbar puncture (after neuroimaging)
Associated to: □Seizures □Recent behavior changes □Declining in school achievement	Intracranial hypertension, intracranial mass lesions, and psychiatric comorbidity	Neuroimaging Psychiatric evaluation
Focal neurologic signs/symptoms	Intracranial hypertension, intracranial mass lesions	Neuroimaging
Exertion-triggered	Subarachnoid hemorrhage, bleed into a mass, AVM, or aneurysm	Neuroimaging
Temporal pattern □Time from onset < 6 months □Worsening-pattern □Change of headache pattern □Worst headache in life	Intracranial hypertension, intracranial mass lesions, arteriovenous malformation, and aneurysm	Neuroimaging
Infection signs/symptoms	Acute sinusitis, meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease, arteritis	Paranasal sinuses CT, lumbar puncture, blood tests
Prominent vomiting	Intracranial hypertension, intracranial mass lesions	Neuroimaging
Sleep disruption by headache	Migraine, Cluster Headache, Hypnic Headache and Intracranial Hypertension	Neuroimaging

THE DIAGNOSIS OF CHRONIC MIGRAINE REQUIRES A STRUCTURED APPROACH

An important first step in diagnosing CM involves excluding secondary headaches that mimic it, and this step is of particular importance in young ages where the transformation phase from episodic into chronic is often very short, and the prevalence of secondary headaches (e.g. to a tumor or infection) is higher relative to adulthood.

Distinguishing CM from secondary headaches require three steps: 1) Obtaining a good history and detailed physical and neurological exam; 2) Looking for red flags; and 3) Investigating properly, as per the red flags.

Step 1- Obtaining a good medical history and detailed physical exam

Without attempts of being reductionists, we affirm that the vast majority of children with frequent headaches in the absence of red flags have migraines. Accordingly, the strategy should focus on spotting red flags as follows (modified from (16)):

- Age of onset and temporal pattern (acute, chronic, progressive, or non-progressive). Look for very early onset (aged younger than 5 years), non-remitting headaches, and rapidly progressive headaches.

- Location of pain when the pain is at its worst. Migraine attacks are either bilateral or unilateral alternating. Totally side-locked headaches should be assessed carefully.

- Relieving and worsening factors during headache attacks. Migraines are typically relieved by compression of the superficial temporal artery, cold compresses on the temples, rest in a dark and silent room, sleep, and vomiting. Migraine is typically worsened by physical activities, but secondary headache is typically worsened as well; therefore, this finding should be interpreted in context.

- A detailed history of medications used, and all the exams performed in the past should be recorded, as well as the degree of functional impact, which may be helpful as a gauge of severity, duration, and frequency of the headaches.

The general physical examination is of particular importance in children with headaches. It should consist of an examination of the skull, including bruits over the temples, mastoids, and orbits. Hemotympanum may be found in head trauma. Measurements should include head circumference, palpation and percussion of sinuses and mastoids, neck, abdomen (palpate for visceromegaly, which can indicate the presence of storage diseases), spine (look for scoliosis and any sacral anomalies), and skin (looking for stigmata of the neurocutaneous syndromes such as café au lait spot and Port-wine stain nevus).

Neurological examination should look for potential signs of ominous disorders and is beyond the scope of this review.

Step 2 – Look for Red Flags

At this point, clinicians should have easily spotted red flags, if there are any. We developed the mnemonic 'S.A.F.E.T.I.P.S.' to help pediatricians to remember what exactly they are looking for:

Sudden-onset headache: when a very severe headache reaches its peak in few seconds or minutes (vs. the more gradual onset of the migraine headaches).

Associated to seizures or to unexplained behavior changes and/or important decline in school achievement.

Focal neurologic signs/symptoms other than typical visual or sensory aura: papilledema (intracranial

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hypertension), sensory or motor deficits, incoordination, and cranial nerves deficits (hearing loss, monocular blindness, visual field deficits, diplopia, strabismus, nystagmus, turning of head, etc).

Exertion-triggered headaches: explosive onset during exercise, coughing, or Valsalva maneuver. Note that what defines the red flag is the intense, fast onset of a headache in close association with these activities. Migraine is often triggered by exercises, but its onset is gradual and its presentation is typical.

Temporal pattern: worsening pattern, important changes in the quality of pain or of its location, or important change in frequency of headaches are red flags. Furthermore, providers should also fear when the complaint is about "the worst headache of the person's life".

Infection signs/symptoms: fever, sore throat, impaired peripheral circulation, petechiae, meningeal irritation (neck stiffness, Kernig's sign, Brudzinsky's sign, and a bulging fontanelle in children with less than 1 year of age).

Prominent vomiting: especially if it doesn't relieve the headaches (which often is observed in migraine) or is delinked from the headaches.

Sleep disruption by headache: children with migraine are often capable of sleeping during the attack and feel relieved by it. Headaches that often wake the children in the middle of the night should be investigated.

In the presence of red flags, the physician must conduct the proper workup or refer the patient to a headache specialist (Table 2). In the absence of red flags, the pediatrician should diagnose and treat the primary headache. The lack of expected improvement or worsening, after proper treatment in proper doses for proper times, is a red flag per se.

We emphasize that obtaining neuroimaging studies in children without red flags is not recommended. Therefore, the 'S.A.F.E.T.I.P.S.' approach should offer good guidance as towhether the clinician should request neuroimaging or other forms of testing.

THE CLINICAL FEATURES OF MIGRAINE IN CHILDREN ARE DIFFERENT THAN THOSE IN ADULTS

Once secondary headaches are excluded, either clinically or after investigation, the physician should be capable of assigning a proper diagnosis of migraine or chronic migraine. Of note, diagnosis is often more difficult in youg ages than in adults because the clinical features are less typical in the pediatric population and, for children below the age of 12, the headache history may be difficult to obtain. Compared to adults, young children with migraine seem to have a higher number of morning attacks or shorter duration of attacks and are more frequently relieved by sleep (17, 18). As children move through adolescence, their migraines begin to resemble migraine in adults. Considering these particularities, we defended that it is illogical to use the same diagnostic criteria to classify adulthood and childhood migraines (19). After intense debate, the International Headache Society acknowledged the often-shorter duration of headaches for patients under age 15 years (1 to 48 hours) than for those over 15 years (4 to 72 hours) and emphasizes that: (1) migraine headache is often bilateral in young children. An adult pattern of unilateral pain often emerges in late adolescence or early adult life; (2) migraine headache is usually frontotemporal in children; (3) in young children, photophobia and phonophobia may be inferred from behavior.

Chronic Migraine Evolves from Episodic Migraine and Risk Factors Have Been identified

A very important aspect of CM that is often missed is that CM doesn't start de novo, it always evolves from episodic migraines. There are frequent headaches that are very frequent from the onset, such as new daily persistent headaches, hemicrania continua, or chronic cluster headaches. But that is not the case of CM.

It is useful, therefore, to conceptualize migraine prognosis as displayed in Figure 2 (based on (20)). With or without therapies and intervention, migraine might remit, be stable, or progress. Once the framework is identified, risk factors for each path can be researched (14). The model is not different than what is used for predictors of age-related cognitive decline, which can be divided in normal, mild cognitive impairment, and dementia (21).

We heavily studied this topic in the population and identified several risk factors for CM in adolescents and

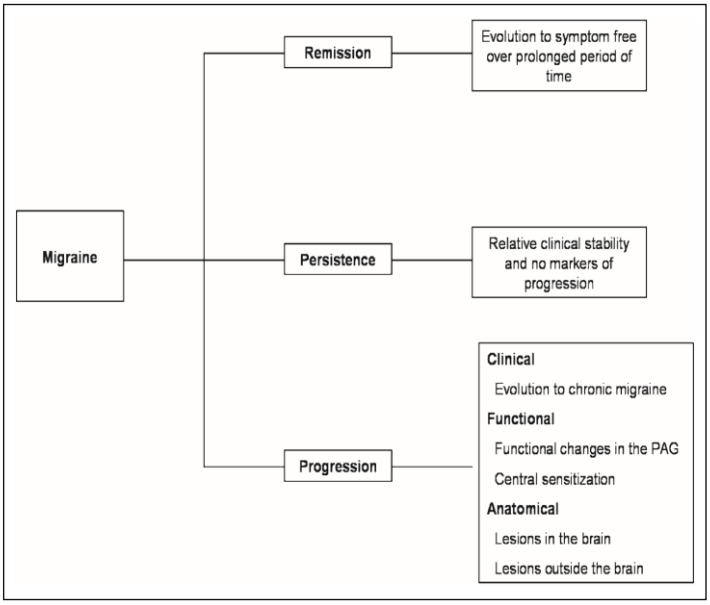

Figure 2- The natural history of migraine (based on (20)).

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adults. We divided these risk factors as modifiable by health intervention and non-modifiable by health intervention. Among non-modifiable risk factors, low income(12) and female sex were prominent. The most relevant modifiable risk factors were excessive acute medication use (to be discussed in further detail later) (5), obesity (22, 23) , allodynia (perception of non-painful stimuli as being painful) (24), other pain syndromes, excessive caffeine intake (25), and depression (26). These risk factors are true for adolescents and adults.

Later in this paper we will emphasize some of these risk factors. However, it is our view that children with CM represent the results of an enhanced biological predisposition rather than a group especially vulnerable to insults. It typically takes multiple years for a patient to transition from episodic to CM, and risk factors play a very important role. However, those who transform quickly and at such a young age are the very predisposed. Despite this, they are often under-treated due to fear of exposing young children to medications perceived as being strong. We have long hypothesized that children with CM would be particularly biologically predisposed and vulnerable. Supporting our hypothesis, we identified risk factors unique to this category, in addition to the overall risk factors (such as obesity and allodynia).

Risk Factor - Frequency of migraine attacks in children are influenced by frequency of attacks in the parents

It is well known that migraines aggregates within families (27, 28), but biological predisposition for migraine frequency in young children has been poorly studied. In the ABP, as compared with negative lifetime family history, any headache history in the mother or in the father increased the relative risk (RR) of episodic (RR = 1.6, 95% CI = 1.3-1.8), or frequent migraines (RR = 6.6, 1.4-28.4) in the children(29). Note that the RR is higher for frequent migraines than for migraines overall.

Not only the presence of migraine, but the frequency of headaches in the mother predicted frequency of headaches in the children. When mother had a low headache frequency, children had an increased chance of experiencing low or intermediate headache frequency (RR = 1.4, 1.2-1.6) but not frequent headaches. When the mother had CM, the risk of CM was increased almost 13-fold in the children, while the risk of infrequent headaches, however, did not rise accordingly. In multivariate models, frequency of headaches in the children were independently predicted by frequency of headaches in the mother after adjustments, suggesting that headache frequency (not only headache status) aggregates in the family (Fig. 3) (29).

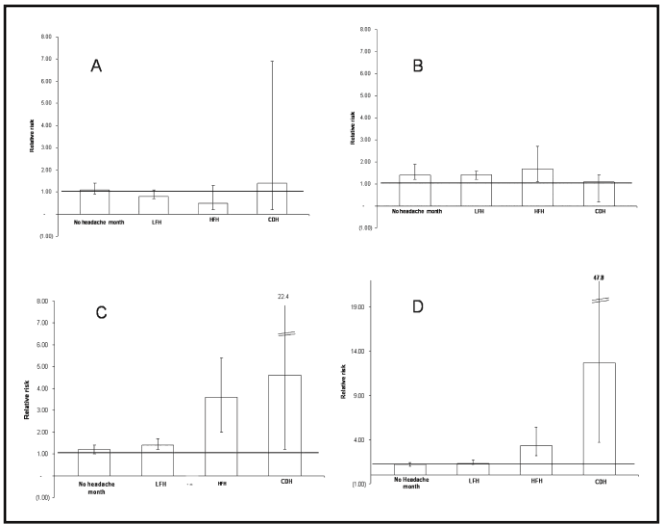

Figure 3- Headache status in children as a function of headache status in the mother, as compared to no headaches in children or mothers. (A) Mother with no headaches during past month; (B) Mother with low frequency episodic headaches; (C) Mother with intermediate or high frequency episodic headaches; (D) Mother with chronic daily headaches. CDH = chronic daily headache; HFH = high frequency headaches; LFH = low frequency headaches (from (49)).

Prenatal Exposures and Risk of Frequent Migraines

As mentioned, increased vulnerability of pediatric subpopulations to certain diseases may reflect a combination of stronger biological predisposition, pre-natal exposures, or early life exposures/comorbidities. We investigated if maternal exposure to tobacco and alcohol were associated with CM in young children, since both exposures target specific neurotransmitter receptors in the fetal brain, predisposing to shortfalls in the number of cells and eventually to altered synaptic activity (30-32). The odds of frequent headaches were significantly higher when maternal smoking was reported, being 2.29 (95% CI = 1.6 vs 3.6) for active smoking (only the mother) and 4.2 (95% CI = 2.1-8.5) for active and passive smoking (the mother and the partner). Alcohol use more than doubled the chance of frequent migraines (24% vs 11%, OR = 2.3, 95% CI = 1.2-4.7). The risk remained significantly elevated after adjusting for family income, parental headache status, medical care during pregnancy, hypertension during pregnancy, and use of illegal drugs.

EXCESSIVE USE OF ACUTE MEDICATION INCREASES THE RISK OF CHRONIC MIGRAINE

For many years, the issue of whether excessive use of acute medication led to increased headache frequency, or whether increased migraine frequency was associated with increased use of analgesics, was heavily debated, but it is now largely settled. Note that this topic is of particular importance for the pediatric population where the natural tendency of the provider is to be less aggressive with treatment, relying more on analgesics and less on

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prophylactic medications. We reviewed this topic in detail elsewhere (33).

In 2008, we published the results of a very large longitudinal study trying to unequivocally assess this topic. The study, which ended receiving the Wolff Award from the American Headache Society included participants aged 12 to 65 years and is still the largest study on the topic(5). Using longitudinal data from the AMPP study, the probability of transition from episodic migraine in 2005 to chronic migraine in 2006 as a function of acute medication use was modeled in multivariate analyses. Several important lessons emerged. First, we found that use of triptans, opioids (mostly analgesics with codeine), and barbiturates (commonly used in the U.S. for the treatment of migraines) were associated with an increased risk of new-onset CM by two-fold. The influence of medication varied according to the baseline headache frequency and drug class. To disentangle the influence of headache frequency and medication use, we adjusted for the number of headache days per month, among other factors, using acetaminophen as a reference group. In these adjusted analyses, those using barbiturates, opiates, or triptans were at increased risk of incident CM compared with those using acetaminophen. Interestingly, non-steroidal anti-inflammatory medications (NSAIDs) were not associated with incident CM. Baseline headache frequency added to the risk for all classes but NSAIDs. The quantitative component was very evident, as illustrated by Figure 4. Risk of CM increased with quantity of medication used per month, and the risks were higher for those with higher frequency of migraine days. Of interest, for triptans, the risk of CM was higher in girls/women than in boys/men in multivariate analyses. These results highlight that prophylactic medication continue to be the mainstream of frequent migraine treatment, with acute medication being used for relief, not overall control.

The Risks of Using Opioids and Tramadol

An important trend seen in recent years in the U.S. was the use of opioids for trivial reasons, and very often being used for headaches. Note that in the definition of opioids, we don't only refer to the classical opioids, such as morphine and its derivatives, which are well-regulated in Brazil, but also to codeine and semi-synthetic opioids such as tramadol, which are considered to be "weaker" and less addictive despite carrying the same potential for increasing headache frequency as most standard opioids.

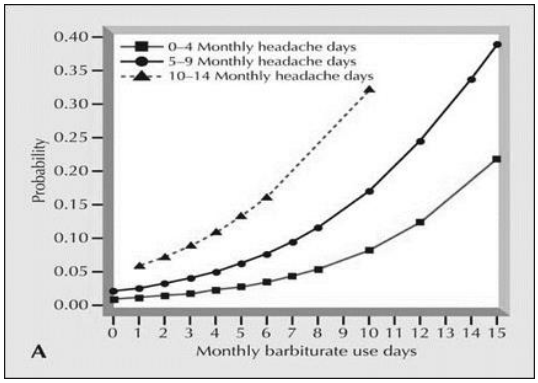

Figure 4- Risk of Chronic Migraine as a function of baseline headache frequency and acute medication use (modified from (5)).

As a first step, one of us (LMB) characterized the prescribing patterns of opioids for any cause (not only for headaches) per U.S. region and physician specialty from 2012-2015 (34) (Table 3). Using the Truven Health Analytics MarketScan®, databases were used to obtain data on opioid prescription rates per U.S. region and physician specialty (35). Opioids included in the study were tramadol, hydrocodone, codeine, oxycodone, oxymorphone, methadone, and fentanyl.

Table 3: Patterns of opioid prescription as a function of prescriber in 2015 and 2012 (modified from (34)).

	Opioid			
Physician Specialty 2015 (2012)	**Tramadol**	**Oxycodone**	**Hydrocodone**	**Fentanyl**
Family Practice	40.1% (43.8%)	20.8% (23.5%)	33.6% (36.8%)	29.6% (30.8%)
Geriatrics	0.1% (0.1%)	0.1% (0.1%)	0.0% (0.1%)	0.1% (0.1%)
Gynecology	4.1% (3.7%)	12.8% (13.0%)	7.0% (8.1%)	1.7% (1.7%)
Internal Medicine	19.8% (20.2%)	13.6% (14.9%)	15.1% (16.2%)	19.6% (22.3%)
Neurology	1.8% (2.15%)	1.5% (1.6%)	1.3% (1.2%)	4.5% (5.0%)
Non-physician prescriber	7.3% (4.7%)	7.0% (4.8%)	7.0% (4.7%)	6.3% (4.2%)
Oncology	0.8% (0.6%)	1.3% (1.2%)	0.9% (0.8%)	8.9% (7.9%)
Pain Medicine	1.8% (1.8%)	2.4% (2.2%)	1.6% (1.1%)	15.4% (14.0%)
Pediatrics	1.1% (0.8%)	2.2% (1.7%)	2.4% (2.3%)	0.8% (0.5%)
Rheumatology	2.5% (2.9%)	0.6% (0.7%)	0.9% (0.7%)	2.5% (2.5%)
Surgery	20.6% (19.2%)	37.6% (36.3%)	30.1% (28.2%)	10.6% (10.9%)

The starting sample consisted of 5,860,096 individuals representative of the U.S. population. An increase in prescriptions was seen for codeine (22.3%), oxycodone (22.4%), and tramadol (22.4%) over the 5-year period (Table 4). Family Medicine physicians were the most frequent prescribers for all opioids except for oxycodone; non-physician prescribers' share of prescriptions nearly doubled for all opioids. The share of oxycodone and of tramadol among all opioids increased in all American regions, while the opposite was seen for hydrocodone. Codeine prescription share increased substantially in the South but not in other regions.

Table 4: Patterns of Tramadol Prescription in 2012 and 2015 in the United States by medical specialty (modified from (35)).

	2012	**2015**
Family practice	43.8%	40.1%
Internal Medicine	20.2%	19.8%
Surgery	19.2%	20.6%
Non-Physician Prescriber	4.7%	7.3%
Other specialties	12.1%	12.2%

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We followed-up by focusing on tramadol, using similar methodology (35). We found that on the top of being prescribed substantially more frequently relative to other opioids ($p < 0.0001$), tramadol was more frequently prescribed by the generalists, including family physicians (40%) and internal medicine physicians (19%). Family medicine, internal medicine, and non-physician prescribers (nurse practitioners and dentists) responded to 67.2% of all tramadol prescriptions in 2015. The proportion of patients receiving tramadol from non-physician prescribers increased by 56% between 2012 and 2015 ($p < 0.001$). A similar phenomenon described was described by an independent group in Canada (36) and in several other settings.(37-39) (Table 4). We suggest that since tramadol (and codeine for this matter) is considered to be less addictive, providers feel more comfortable prescribing it relative to other opioids.

A NOTE ABOUT OBESITY

Obesity has been established without a reasonable doubt as a risk factor for CM. It does not increase the chances of episodic migraine (40), but it substantially increases the chance of increased headache frequency and of CM (23, 41). Among individual migraine, very frequent headaches (10-14 d/mo) occurred in 7.4% of the overweight ($P=.10$), 8.2% of the obese ($P< 0.001$), and 10.4% of the severely obese ($P< 0.0001$) subjects, compared to 6.5% of those with normal weight. Similar ratios were seen for CM. Therefore, obesity is a powerful risk factor for frequent headaches. It needs to be avoided, treated, and not induced by lack of monitoring after using migraine medications with potential for weight gain (eg flunarizine).

THE TREATMENT OF CHRONIC MIGRAINE

Describing the treatment of frequent migraines in detail is beyond the scope of this paper, and we reviewed the topic extensively elsewhere (42). Herein we just summarize some useful principles for the practicing physician.

Being complex and associated with multiple risk factors, treating CM requires a structured approach, summarized in the following steps (modified and updated from (42)):

Step 1 – Reassure and engage the children and the family. Children with CM and their parents often fear ominous causes for the child's headache, especially when it occurs chronically and daily. After being educated and reassured about the diagnosis and the preventable and remissible nature of the disease, they can really cope better and actively adhere to any treatment proposal.

Step 2 –Take advantage of non-pharmacological measures, including: (1) Encouraging the use of a headache diary to demonstrate improvement. A child that moves from 30 to 25 days of headache per month may fail to perceive improvement and disengage. The diary reinforces the concept that treatment is working; (2) Employ cognitive/behavioral therapies when appropriate, including biofeedback, relaxation training, behavioral management programs, stress management, and cognitive coping skills; and (3) Monitor risk factors for migraine, including obesity, and encourage maintenance of normal weight.

Step 3 – Screen and treat comorbidities that may make the treatment of frequent migraines more difficult, including allergies, depression, anxiety, sleep disorders, and others.

Step 4 – Use pharmacological treatment, stratified:

Acute treatment. The most important principle to follow in the acute treatment of CM is to avoid medication overuse. However, in the course of CM treatment, more severe attacks must be adequately treated by choosing a proper medication. The main goal should be the rapid return to normal activity without relapse. The appropriate and tailored dosage for children is recommended and the attacks should be treated as soon as possible. For acute treatment in the pediatric population, level 1 evidences are reported for the following: ibuprofen and acetaminophen (down to age 4), rizatriptan PO, sumatriptan IN, and zolmitriptan PO (from 6 to 17 years of age), and almotriptan (from 12 to 17 years of age) (16). When headaches are mild to moderate and nausea is present, we associate the NSAID with anti-emetic medications. Our choice is piroxicam (level II-1 evidence) or ketorolac tromethamine sublingually (level III evidence), given their rapid absorption, fast onset of action, efficacy, and safety. For children with more debilitating attacks, triptans are our drugs of choice. Compounds with caffeine, barbiturates, and narcotics should be avoided in the primary care treatment of migraine.

Preventive treatment is the mainstream of CM treatment, and we offer the following principles: (1) When possible, always treat within label by giving preference to approved drugs; (2) When evidence is not available, or when first-line therapies have failed, select a drug based on plausibility, proven efficacy in studies with adults, and proven safety in children. Our choice is largely based on the potential to use the drug profile to address comorbid conditions, such as: (a) Topiramate for children with obesity; (b) Topiramate, divalproate, or levetiracetam for epileptic children; (c) Amitriptyline for children with hyporexia, depressive disorder, and/or nocturnal enuresis. Beta-blockers and calcium-channel blockers are also effective, although they seem to be less effective in the most severe forms of migraine.

More recently, based on the establishment that calcitonin gene-related peptide (CGRP) is a peptide of importance not only for migraine, but for the development of chronic migraine,(43) several monoclonal antibodies anti-CGRP were developed, including one (fremanezumab) by one of us (MEB). Fremanezumab demonstrated efficacy as monthly and quarterly sub-cutaneous doses both in episodic (44, 45) and chronic migraine (46, 47). Fremanezumab has

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been tested in the pediatric population.(48) Although we don't advocate using these expensive, novel therapies as first line, we certainly see their role in the treatment of very refractory children.

CONCLUSION

In summary, CM is frequent in the pediatric population and risk factors include prenatal exposure to tobacco, age at migraine onset, paternal headache history, maternal headache frequency, obesity, and analgesic abuse. Of the acquired risk factors, the most robust seem to be obesity and headache frequency. The management of CM involves prevention of its establishment in the first place by adequate diagnosis and care for children with episodic migraine. In children with established CM, we suggest aggressive preventive treatment and medications with reasonable evidence.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was not required for this study

Conflict of interest

The authors declare no conflicts of interest with respect to the content, authorship, and/or publication of this article.

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Contribution

Luisa Bigal: drafting first version and editing the manuscript

Renato Arruda: data collection and manuscript review

Marco Arruda : data collection and manuscript treview

Marcelo E. Bigal: overseeing the manuscript concept and outline, manuscript review

REFERENCES

1. 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.
2. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. Neurology. 2004;63(3):427-35.
3. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology. 1996;47(4):871-5.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
5. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache. 2008;48(8):1157-68.
6. Bigal ME, Buse DC, Chen YT, Golden W, Serrano D, Chu MK, et al. Rates and predictors of starting a triptan: results from the American Migraine Prevalence and Prevention Study. Headache. 2010;50(9):1440-8.
7. Bigal ME, Borucho S, Serrano D, Lipton RB. The acute treatment of episodic and chronic migraine in the USA. Cephalalgia. 2009;29(8):891-7.
8. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.
9. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Childhood periodic syndromes: a population-based study. Pediatr Neurol. 2010;43(6):420-4.
10. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Migraine, tension-type headache, and attention-deficit/hyperactivity disorder in childhood: a population-based study. Postgrad Med. 2010;122(5):18-26.
11. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Primary headaches in childhood--a population-based study. Cephalalgia. 2010;30(9):1056-64.
12. Bigal ME, Lipton RB, Winner P, Reed ML, Diamond S, Stewart WF, et al. Migraine in adolescents: association with socioeconomic status and family history. Neurology. 2007;69(1):16-25.
13. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Frequent headaches in the preadolescent pediatric population: a population-based study. Neurology. 2010;74(11):903-8.
14. Bigal ME, Ferrari M, Silberstein SD, Lipton RB, Goadsby PJ. Migraine in the triptan era: lessons from epidemiology, pathophysiology, and clinical science. Headache. 2009;49 Suppl 1:S21-33.
15. Lipton RB, Bigal ME. Ten lessons on the epidemiology of migraine. Headache. 2007;47 Suppl 1:S2-9.
16. Bigal MEA, M.A. Headaches and Migraines. In: Feld LGM, J.D., editor. Succint Pediatrics - Evaluation and Management for Common and Critical Care. United States: American Academy of Pediatrics; 2015. p. 275-96.

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17. Winner P. How do we diagnose migraine and childhood periodic syndromes? Curr Pain Headache Rep. 2005;9(5):345-50.
18. Bigal ME, Arruda MA. Migraine in the pediatric population--evolving concepts. Headache. 2010;50(7):1130-43.
19. Bigal ME, Rapoport AM, Tepper SJ, Sheftell FD, Lipton RB. The classification of chronic daily headache in adolescents--a comparison between the second edition of the international classification of headache disorders and alternative diagnostic criteria. Headache. 2005;45(5):582-9.
20. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. Neurology. 2008;71(11):848-55.
21. Derby CA, Katz MJ, Lipton RB, Hall CB. Trends in Dementia Incidence in a Birth Cohort Analysis of the Einstein Aging Study. JAMA Neurol. 2017;74(11):1345-51.
22. Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. Neurology. 2007;68(21):1851-61.
23. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology. 2006;67(2):252-7.
24. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology. 2008;70(17):1525-33.
25. Scher AI, Stewart WF, Lipton RB. Caffeine as a risk factor for chronic daily headache: a population-based study. Neurology. 2004;63(11):2022-7.
26. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, et al. Depression and risk of transformation of episodic to chronic migraine. J Headache Pain. 2012;13(8):615-24.
27. Russell MB. The genetics of migraine. Eur J Neurol. 1997;4(1):2-7.
28. Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Happola P, Mitchell AA, et al. Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families. Neuron. 2018;99(5):1098.
29. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Frequency of headaches in children is influenced by headache status in the mother. Headache. 2010;50(6):973-80.
30. Handmaker NS, Rayburn WF, Meng C, Bell JB, Rayburn BB, Rappaport VJ. Impact of alcohol exposure after pregnancy recognition on ultrasonographic fetal growth measures. Alcohol Clin Exp Res. 2006;30(5):892-8.
31. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther. 1998;285(3):931-45.
32. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Prenatal exposure to tobacco and alcohol are associated with chronic daily headaches at childhood: A population-based study. Arq Neuropsiquiatr. 2011;69(1):27-33.
33. Bigal ME, Lipton RB. Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep. 2009;13(4):301-7.
34. Bigal LM, Bibeau K, Dumbar S. Patterns in opioid prescription in the United States by region and prescribers over a 4-year period. J Opioid Manag. 2019;15(6):499-506.
35. Bigal LM, Bibeau K, Dunbar S. Tramadol Prescription over a 4-Year Period in the USA. Curr Pain Headache Rep. 2019;23(10):76.
36. Smolina K, Gladstone E, Morgan SG. Determinants of trends in prescription opioid use in British Columbia, Canada, 2005-2013. Pharmacoepidemiol Drug Saf. 2016;25(5):553-9.
37. Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration's Rescheduling of Hydrocodone Combination Analgesic Products on Opioid Analgesic Prescribing. JAMA Intern Med. 2016;176(3):399-402.
38. Oehler EC, Day RL, Robinson DB, Brown LH. Has the rescheduling of hydrocodone changed ED prescribing practices? Am J Emerg Med. 2016;34(12):2388-91.
39. Schultz S, Chamberlain C, Vulcan M, Rana H, Patel B, Alexander JC. Analgesic utilization before and after rescheduling of hydrocodone in a large academic level 1 trauma center. J Opioid Manag. 2016;12(2):119-22.
40. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. Neurology. 2006;66(4):545-50.
41. Bigal ME, Rapoport AM. Obesity and chronic daily headache. Curr Pain Headache Rep. 2012;16(1):101-9.
42. Arruda MA, Chevis CF, Bigal ME. Recent advances in the management of chronic migraine in children. Expert Rev Neurother. 2018;18(3):231-9.
43. Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. Headache. 2013;53(8):1230-44.
44. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1081-90.
45. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018;319(19):1999-2008.
46. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091-100.

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47. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017;377(22):2113-22.
48. Cohen-Barak O, Radivojevic A, Jones A, Fiedler-Kelly J, Gillespie M, Brennan M, et al. Dose selection for fremanezumab (AJOVY) phase 3 pediatric migraine studies using pharmacokinetic data from a pediatric phase 1 study and a population pharmacokinetic modeling and simulation approach. Cephalalgia. 2021;41(10):1065-74.
49. Arruda MA, Bigal ME. Migraine and behavior in children: influence of maternal headache frequency. J Headache Pain. 2012;13(5):395-400.

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