Chapter 20
Pharmacological Treatment of Headache and Comorbidities

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20.1 Introduction

The term "headache" encompasses primary conditions and those secondary to other illnesses. This chapter describes the pharmacotherapy of primary headaches in children affected by additional diseases. As in the adult population, the most common primary headaches in children are migraine and tension-type headaches. Overall, the international prevalence of migraine among children and adolescents is in the range of 7.7–9.1%. Migraines are more prevalent in girls than boys when the age is 12 years or older, and migraine with aura is less common than migraine without aura [1–3]. Chronic migraine in US adolescents aged 12–17 years was 0.79, and 2% when including medication overuse [4]. Using a dedicated questionnaire, a population of children from 6 to 17 years of age exhibited the following 1-year prevalence: headache 89.3%; migraine 39.3%; and tension-type headache (TTH) 37.9%. Headache prevalence ≥15 days/month was 4.5% [5]. Cluster headache (CH) is a rare condition in adults and even rarer in children, with prevalence in the pediatric population estimated as 0.03–0.09% [6, 7]. In particular, attention is paid to pharmacotherapy of comorbidity of migraine with other diseases. Comorbidities affect treatment strategy and follow-up, especially when pharmacologic treatment is needed. In this chapter, we summarize pharmacologic options for migraine and tension-type headache treatment with specific attention to comorbidities.

The therapy of childhood migraine is based, like that for the adult population, on algorithms including behavioral approaches, abortive drugs, and preventative strategies, as well as non-pharmacological options (alternative and complementary

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medicines) such as vitamins, supplements, and drugs. Pharmacotherapy is rather complex as the use of some medicines is not based on formal randomized clinical trials, and, therefore, in clinical practice, most choices are "off label." However, in this respect, comorbidities may increase the appropriateness of treatment as certain drugs may be approved not for migraine but for the comorbid condition.

20.2 Abortive Migraine Treatment

Comorbidities do not significantly impact abortive migraine treatment, which is mainly based on the use of analgesics (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans. Abortive (rescue) medications are taken during acute headache attacks, with the goal of providing quick relief from headache pain. The use of these medications should be limited to not more than 10 or 15 (depending on the type of drug) doses per month, to avoid medication overuse headache. Early recognition and treatment, and resting in a quiet location after drug intake, are key points for successful treatment of migraine attacks. All medications have a better chance of relieving symptoms if given as early as possible in the attack. Gastroparesis frequently occurs as migraine sets in, limiting the absorption of oral medications.

For some pediatric patients, over-the-counter (OTC) analgesics provide sufficient relief, are well tolerated, and have little or no side effects. Acetaminophen and ibuprofen are more likely than placebo to reduce headache intensity at 2 h posttreatment, are safe and effective in migraine, and are recommended as first-line therapy, especially when doses are weight based [8]. Other nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, may provide relief from migraine pain, especially for prolonged attacks. NSAIDs are not recommended or must be used carefully in patients with gastrointestinal (such as inflammatory bowel syndrome or gastric ulcer), cardiovascular (arterial hypertension), or severe allergic (asthma) comorbidities.

Among abortive medicines, triptans have been the most extensively studied. They might work by reversing the cranial artery dilation (via $5HT_{1B}$ receptor activation on vascular smooth muscle) that occurs during migraine or by inhibiting the release of calcitonin gene-related peptide (CGRP) (via $5HT_{1D}$ receptor activation on nerve terminals) from trigeminal nociceptors. Triptans are migraine-specific acute abortive agents and are considered to be most effective when given early in the course of the headache. While in adults all triptans have level A evidence for efficacy [9], the same level of efficacy has not been reported in children [10], probably because of a higher placebo response and the shorter duration of attacks in the pediatric population. They are typically administered by the oral route, although nasal sprays are also available. The intranasal route may be preferable in patients who have significant vomiting with their migraines. Sumatriptan is available in an injectable preparation; however, it is seldom used in pediatric practice. Triptans approved for treatment of pediatric migraine are rizatriptan (6–17 years old), almotriptan (12–17 years old), and a combination of sumatriptan and naproxen (12–17 years old).

A multicenter, randomized, double-blind, placebo-controlled study found no difference in pain relief at 2 h when comparing oral sumatriptan to placebo [11], but another study found that a sumatriptan (20 mg nasal spray) provided greater rates of relief at 30 min and 2 h post-dose compared to placebo [12]. Zolmitriptan has been shown to provide fast relief when given in nasal spray form, with onset of pain relief often apparent within 15 min [13], whereas oral ibuprofen provided rates of pain relief at 2 h similar to placebo [14]. Eletriptan and placebo do not differ significantly in headache improvement at 2 h, although eletriptan reduced headache better than placebo in the 24 h post-dose [15]. When using triptans, patients and their parents should be advised of possible adverse effects, such as chest tightness, drowsiness, dizziness, and, rarely, serotonin syndrome (mostly in children taking SSRIs or SNRIs) [16].

Dihydroergotamine is a nonselective vasoconstrictor agent mainly used before triptans were available. Side effects, mainly due to their nonselective agonist action on 5-HT1 and 5HT2 receptors and dopamine D2 and alpha-adrenergic receptors, are more common and severe than with triptans. In children, a spray formulation of dihydroergotamine might be considered if triptans are ineffective. Butalbital-containing medications are rarely used because of the risk of development of medication overuse headache if taken more than twice weekly [17]. There are no randomized controlled trials in adults or children to support the efficacy of opioids in migraine, so they should not be used in the treatment of primary headaches, also because they are associated with the risk of medication overuse headache and with the transformation from episodic to chronic form. Steroids, such as dexamethasone, should be used (administered for a few days) for terminating a status migrainosus. In addition to analgesic medication drugs for nausea, including ondansetron (used principally in the emergency room), metoclopramide and prochlorperazine can be considered [18].

20.3 Preventive Migraine Treatment

Preventive medications are usually taken when the headaches occur more than once per week, causing frequent disability. The goal of preventative medication is to relieve pain and reduce disability from headache. Parents should be informed about the aims of this therapy (e.g., a 50% reduction in headache frequency and severity), the duration of the treatment (a positive effect will not be appreciated in a short time but rather after weeks or months), and the appropriate regimens of drug administration associated with lifestyle modifications. Notably, a high placebo response rate in adolescents makes interpretation of the limited available evidence rather difficult. It should be clarified that to reduce overall migraine frequency and severity, maintenance therapy should usually be taken on a daily basis. It is also important to set realistic expectations as maintenance therapy usually does not eliminate headaches completely. The combination of daily prophylactic therapy, periodic use of an abortive medication, and lifestyle modification seems to achieve better results [19].

Vitamins, minerals, and supplements have been proposed as prophylactic agents, popular with parents who believe them to be safer than drugs [20]. Riboflavin (vitamin B2), used in adults for migraine prophylaxis, has limited and mixed evidence in the pediatric population. One randomized, double-blind, placebo-controlled study reported a similar proportion of 50% or greater reduction in headache frequency by both riboflavin (400 mg/daily) and placebo groups, with some side effects of riboflavin (strong odor/color of urine and mild gastrointestinal upset) [21]. Magnesium, which regulates cellular and neuronal homeostasis, is frequently used for migraine prevention in children at a dose of 9 mg/kg/day [22], with diarrhea as the most frequent adverse effect. Coenzyme Q10 is an electron carrier involved in mitochondrial energy production and is used in children and adults, usually at 1–3 mg/kg/day. Butterbur extract (*Petasites hybridus*) is recommended in adults for migraine treatment for its anti-inflammatory and perhaps neuromodulatory effects. In an open-label study, 108 children and adolescents between 6 and 17 years of age were treated with 50–150 mg of butterbur root extract; 77% of them reported a reduction in the frequency of migraine attacks by at least 50%. Undesired effects (7.4%) included mostly eructation [23]. Feverfew (*Tanacetum parthenium L.*) belonging to the Asteraceae family is an herbal remedy for migraine [24, 25] that may act via several mechanisms of action, including inhibition of nociception and neurogenic vasodilatation in the trigeminovascular system by targeting the transient receptor potential ankyrin (TRPA1) channel [26]. However, no trials report the safety or efficacy profile of feverfew for pediatric headache [27]. Vitamin D supplementation, associated with migraine prophylaxis, has been shown to reduce headache frequency [28]. Currently, among the various preventive pharmacological treatments in adults, only topiramate is approved for migraine prevention in children. This anticonvulsant agent reduced mean monthly headache frequency and school absenteeism better than placebo and produced a greater reduction in headache-related disability, measured by the Pediatric Migraine Disability Assessment Scale (PedMIDAS) [29]. In another study, topiramate resulted to be more effective than propranolol in reducing headache frequency, severity, duration, and disability [30]. Possible adverse events are cognitive slowing, weight loss, and paresthesias. However, a very recent large study (Childhood and Adolescent Migraine Prevention, CHAMP) [31] comparing the effectiveness of amitriptyline, topiramate, and placebo showed no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks, but the active drugs were associated with higher rates of adverse events. The calcium channel blocker flunarizine significantly reduced frequency and duration of migraine attacks in two double-blind trials after treatment, respectively, of 4 and 8 months [32, 33]. Other studies confirmed the efficacy of this drug at a dose of less than 5 mg oral/day in children 6–11 years of age [32]. Other medications that are commonly used for migraine prevention, such as cyproheptadine and divalproex sodium, do not have sufficient evidence to be recommended for children. Pizotifen is widely used as prophylaxis in children with migraine, but there are no trials assessing its efficacy [32].

Both valproate and propranolol, a nonselective beta-blocker, have been shown to be effective in reducing monthly headache frequency by >50% and to cause a statistically significant reduction in headache severity and mean headache duration per week, as well as an improvement in response to rescue medications [32]. Propranolol should be avoided or used with great caution in patients with asthma, as it can cause bradycardia and hypotension. Valproate should be avoided in young women of childbearing age due to its potential teratogenicity and weight gain. While gabapentin has not been extensively studied in the pediatric population, it may be helpful in the management of selective subpopulations. There are anecdotal reports of some benefits in patients treated with low doses of amitriptyline, with a warning of possible drowsiness, QT prolongation, and suicidal ideas. The antihistamine cyproheptadine in a syrup form might be useful in younger migraineurs with the advantage of easy use in children unable to swallow pills. Possible side effects are weight gain and drowsiness [32]. Verapamil, levetiracetam, pregabalin, and zonisamide have also been used in the treatment of migraine, but there is little evidence supporting their use in the pediatric population [34, 35].

Generally, treatment should be started with a low dose that may be gradually increased for a trial of 4–6 weeks at a target dose. If there is no change in headache burden by that time, a change to an agent of a different class should be adopted. Combination of two or more prophylactic drugs is uncommon. Should a good control of headaches be attained, treatment can be continued for at least 3–6 months before considering its tapering [36, 37].

20.4 Psychiatric Conditions and Headache

Depression and anxiety are not as rare as once thought in children. Mood disorders, attention-deficit/hyperactivity disorder, and obsessive-compulsive disorder can increase migraine severity, and, vice versa, migraine can exaggerate mood disorders [38–40]. For both chronic migraine and chronic tension-type headache, in addition to psychological interventions, such as cognitive behavioral therapy, antidepressants, including selective serotonin reuptake inhibitors (SSRIs), especially fluoxetine, sertraline, and fluvoxamine, can be used for treatment. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are not as effective as SSRIs. Amitriptyline is one of the most widely used prophylactic medications in pediatric migraine, although its efficacy has not been assessed in randomized controlled trials. Starting doses of 5–12.5 mg once daily may be gradually increased to 1 mg/kg/day. Due to its side effects, most notably somnolence, amitriptyline must be titrated slowly over a period of 8–12 weeks, increasing by 0.25 mg/kg/day every 2 weeks or so. Nortriptyline, with its less sedating effects, is sometimes used to replace amitriptyline, although it does raise the concern for increased risk of arrhythmia, and regular electrocardiograms may need to be performed. Beta-blockers are not good options for long-term treatment of migraine coexisting with depression.

20.5 Sleep Disorders and Headache

The coexistence of sleep disorders and headache, particularly migraine, is related to common anatomical structures and neurochemical processes. Treatment of sleep disorders, including insomnia, sleep apnea, sleep bruxism, and restless leg syndrome, often decreases the frequency and intensity of migraine [41]. Dietary changes and sleep hygiene, stress management, reassurance, biofeedback, and behavioral therapies are non-pharmacologic preventive methods in children with migraine. Antihistaminics, melatonin, and serotoninergic drugs are the first options in pharmacologic treatment. Cyproheptadine, an antihistamine with anti-serotoninergic properties, has been widely prescribed for pediatric migraine since the 1980s, although efficacy data are limited. It is often prescribed in doses of 0.2–0.4 mg/kg/day and is considered a first-line option for children under the age of 6 years. It has the added benefit of coming in a liquid form for those who have difficulty swallowing pills. The most commonly encountered side effect, which is sedation, can be used to treat children with concomitant sleep disorders. Drugs containing caffeine are not recommended in the pediatric population.

20.6 Epilepsy and Migraine

The migraine-epilepsy continuum covers a fascinating array of disorders that share many clinical similarities but also differ fundamentally in pathophysiology. Both conditions are episodic neurological disorders, can be triggered, and have similar attack evolution stages. Treatment of migraine and seizures with antiepileptic drugs as topiramate and valproic acid is effective [42]. The effective dose of topiramate in the pediatric population has not been established, but a dose of 2–4 mg/kg/day appears to be effective. To achieve this dose, however, it must be titrated slowly, typically increasing the dose by quarter steps over a period of 8–12 weeks. The most commonly observed side effects include drowsiness, paresthesias, memory or language dysfunction, decreased appetite and anorexia, metabolic acidosis, hyperthermia, dizziness, and abdominal pain. Valproic acid is another migraine prevention considered first-line in adults, and several open-label and retrospective studies have suggested that it may be effective in children and adolescents. Doses of 15–20 mg/kg/day appear to be effective and must be titrated over a period of 8–12 weeks to avoid unwanted side effects. Adverse effects include dizziness, drowsiness, alopecia, weight gain, thrombocytopenia, lymphopenia, potential hyperammonemia, and elevated pancreatic enzymes that make laboratory surveillance critical.

Gabapentin, pregabalin, zonisamide, and levetiracetam can also be used as second-line treatments. In particular, levetiracetam (500–1500 mg bid), in view of its relatively desirable safety profile, with irritability, aggressiveness, and mild memory issues as the most reported adverse effects, has been considered a reasonable alternative option. As tricyclic antidepressants (TCAs) can decrease the seizure threshold, the use of drugs such as amitriptyline, imipramine, mianserin, clomipramine, and maprotiline requires caution if an epileptic disorder is present.

20.7 Atopic Disorders and Migraine

Trigeminal nociceptors can be activated by allergens by releasing inflammatory chemicals from dural mast cells, and this can trigger a migraine attack. We know that glyceryl trinitrate (a donor of nitric oxide (NO)) and histamine (which probably activates endothelial NO formation) both cause a pulsating dose-dependent headache with several migrainous characteristics. Sinus pathologies can coexist with migraine and tension-type headache, and their diagnostic criteria sometimes overlap [43, 44], making differential diagnosis difficult. Antihistaminics, steroids, and antibiotics can be added to the standard treatment procedure in headaches coexisting with atopic disorders. Beta-blockers must be excluded from the treatment because of their capacity of obstruction at bronchial level.

20.8 Obesity and Headache

Childhood obesity can be associated with many medical disorders, such as diabetes, cardiovascular disease, and mood disorders. Tension-type headache and migraine can also coexist with obesity. Research data have highlighted that there is a relationship between headache physiopathology and central and peripheral mechanisms responsible for food assumption. In this regard, neurotransmitters such as serotonin and peptides such as orexin and adipocytokines (adiponectin and leptin) seem to play a key role both in food assumption and in headache pathogenesis. Therefore, those therapeutic strategies aiming to decrease body weight may represent a model of useful treatment to understand whether weight loss reduces the incidence and the severity of headache in obese children [45]. Weight loss, regular diet, and physical exercise (although sometimes intense exercise can trigger migraines) are the first line of treatment. Having a weight loss side effect, topiramate is a good option for overweight and obese migraine patients. Norepinephrine dopamine reuptake inhibitor (NDRI) antidepressants can cause weight loss, and bupropion can be used in both migraine and tension-type headache treatment.

20.9 Cardiovascular Disease, Ischemic Stroke, and Headache

The mean annual incidence of stroke in children is about 2.5 per 100,000 [46]. The causes of cerebral infarction in children may include: heart disease, vascular disease, blood disorders, primary hypercoagulable states, or congenital metabolic disorders, but 50% of strokes are considered idiopathic [47]. In children, the diagnosis of stroke caused by migraine is still questioned; in fact, until now, only a few cases have been reported in subjects under the age of 16 years [48, 49]. A history of migraine with aura seems to be more common among victims of ischemic stroke than among controls, and an acute attack of migraine may precede, accompany, or follow a

thromboembolic transient ischemic attack or a stroke, this seems to occur more often among migraineurs compared with patients without migraine [50, 51]. Adults suffering from migraine with aura are at increased risk of cardiovascular disease and stroke [52], but it is necessary to consider that in adults, the analysis of this association is complicated by a frequent presence of additional risk factors such as smoking, hypertension, and diabetes mellitus. In children, these and other potential confounding factors are much less common. There are relationships arising from small clinical samples of pediatric age who demonstrate the association of migraine with dyslipidemia [53], hyperhomocysteinemia, and genetic variants related to homocysteine which appear to be risk factors for the development of stroke in children [54]; for this reason, these risk factors should be kept under control. Beta-blockers, most notably propranolol with suggested dosing ranging from 0.5–2 mg/kg/day, are the first option for migraine patients having arrhythmias. Its usefulness in this population is limited by a drop in blood pressure as well as exercise-induced asthma and depressive side effects, but it can be useful if there is a heart rhythm disorder. Tricyclic antidepressants can cause arrhythmias, so TCAs must be excluded from treatment.

20.10 Brain Tumors and Headache

A careful history and physical examination remain the most important aspects of headache assessment, enabling the specialist to decide if any further studies are necessary. Imaging of headache patients for tumors, if they have primary headache disorders, such as migraine and typical cluster, generally is not cost-effective but is necessary if there are any atypical features. However, only a minority of patients who have headaches have brain tumors; however, recognition of the headaches characteristically associated with tumors is most important. Some locations are more likely to produce headache (e.g., a posterior fossa tumor causes headache more often than a supratentorial tumor). Rapidly growing tumors are more likely to be associated with headache. Uncommon headache presentations can occur with tumors, including paroxysmal cough, cluster headache, and TACs. The classic brain tumor headache is not as common as a tension-type presentation or migraine. Patients who have prior primary headaches may have more headache symptoms if they have a tumor and of course they still have their primary headache disorder. Mass lesions progress and inevitably develop other symptoms and signs besides headache, and these new symptoms and signs must be sought and found. Treatment of headache in patients who have metastatic brain tumors should be aggressive in terms of pain and symptoms control. Treatment of primary CNS tumors is dictated by the kind of neoplasm and site, but control of headache should not be ignored; for this reason, standard treatment protocols can be combined with steroids and antiemetics. Antiepileptic drugs may be a first choice in patients with migraine and brain tumor to reduce seizure risk. Conversely, TCAs must be excluded from treatment because of their capacity of lower seizure threshold.

20.11 Movement Disorders and Headache

Tourette syndrome is one of the most common childhood movement disorders. It is characterized by motor and phonic tics. Neurotransmitter dysregulation, particularly involving the serotonin system, has been implicated in the pathogenesis of Tourette syndrome, obsessive-compulsive disorder, and migraine headache. The rate of migraine in this group of patients is four times more, and tension-type headache is five times more [55]. Antiepileptics (carbamazepine, phenytoin, valproate), beta-blockers, and SSRIs can be used in the treatment of patients with Tourette syndrome and migraine, whereas TCAs are the option for tension-type headache treatment. Antiemetics are not recommended.

20.12 Autism Spectrum Disorders and Headache

Autistic children that are overreactive to sensory input also have anxiety behaviors and frequently experience both migraine headaches and tension-type headaches. Both migraineurs and autistic individuals have elevated levels of serotonin [56].

Antidepressants (SSRIs), antiepileptics (carbamazepine, valproate), propranolol, and melatonin can be used for the treatment of migraine, and antidepressants (SSRIs) can be used for the treatment of tension-type headache.

20.13 Fibromyalgia and Headache

Many people who have fibromyalgia may also have tension-type headache, migraine, anxiety, and depression [57]. Similar to migraine, changes in the levels of serotonin may contribute to the increased excitation in fibromyalgia. Also, levels of substance P are high in patients with fibromyalgia. Amitriptyline and SSRIs are the first line of treatment in both migraine and tension-type headache.

20.14 Learning Disabilities and Headache

Learning disabilities and attention-deficit/hyperactivity disorder (ADHD) can frequently be observed in children and adolescents and often coexist with primary headaches [58]. Dopaminergic system dysfunction, brain iron deficiency, and sleep disturbance may play a role in both conditions. Antidepressant drugs and melatonin are the first options in pharmacological treatment.

20.15 Rheumatic and Autoimmune Diseases and Headache

There is a higher prevalence of migraine and tension-type headache in patients with juvenile idiopathic arthritis and familial Mediterranean fever. This can be due to the nonspecific result of stress associated with the disease chronicity, or headache can be triggered by the immune-mediated disease activity [59]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids can be used alone or in combination with the standard treatment protocols.

20.16 Emerging Therapies

Both physicians and patients are often frustrated with the current therapeutic options for primary headache and particularly for the chronic forms that represent a major unmet medical need. Moreover, approximately 3% of pediatric migraineurs fall into the chronic migraine category, many of whom are intractable and have failed two or more preventive medications.

Onabotulinum toxin A was approved by the FDA in 2010 for use in chronic migraine in adults, but data on effectiveness and tolerability in the pediatric population are limited. In a retrospective case series to assess tolerability and efficacy of onabotulinum toxin A in 10 patients aged 11–17 years, four patients reported subjective but clinically meaningful relief consisting of a decrease in headache intensity, with two patients additionally noting a decrease in headache frequency. The four responders also reported improvements in quality of life [60]. In another retrospective review of pediatric patients receiving onabotulinum toxin A for chronic migraine, a statistically significant improvement in monthly headache frequency was found [61]. A 30-point improvement in the pediatric disability scoring between first injection and follow-up injection was also observed, with a change from severe disability to moderate disability on PedMIDAS.

Eventually, the current large number of clinical trials with monoclonal antibodies against CGRP (the pro-inflammatory and vasodilator neuropeptide released from terminals of trigeminal neurons) or against its receptor [62] will provide final data regarding this innovative approach to treat migraine and cluster headache. The expectation is that this therapy may also be applied to the pediatric population soon (Table 20.1).

Table 20.1 Summary for recommended treatment of comorbidities

Comorbidity treatment	Recommended	Unrecommended
Psychological conditions	SSRIs	Beta-blockers
Sleep	Antihistaminics, melatonin, seratoninergic drugs	Caffeine
Epilepsy	Antiepileptics	TCAs
Atopic disorders, allergic rhinitis	ST with antihistaminics, steroids	Beta-blockers
Obesity	Topiramate, NDRIs, SSRIs	TCAs, mirtazapine
Cardiovascular disease, ischemic stroke	Beta-blockers, antiplatelet agents	TCAs
Brain tumors	Antiepileptics, SSRIs	TCAs
Movement disorders	Antiepileptics, antidepressants, beta-blockers	Antiemetics
Autism spectrum disorders	ST	
Fibromyalgia	SSRIs	
Learning disabilities	SSRIs	Antiepileptics
Chronic rheumatic disease	ST with NSAIDs and/or steroids	

ST standard treatment

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