Prophylactic drug treatment of migraine in children and adolescents: an update

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Abstract

Migraine as a highly disabling pain condition influences the daily activities of those affected, including children and adolescents.
The pathomechanism of migraine is not fully understood, and the different types of prophylactic antimigraine drugs that are applied are not specific for migraine. There is a need for preventive treatment in the event of frequent migraine attacks, an impairment of the quality of life, severe accompanying or aura symptoms, and the failure of acute drug treatment. The following pharmacological classes are recommended: antidepressants, antiepileptics, antihistamines, beta-adrenergic receptor blockers and calcium ion channel antagonists, besides onabotulinum toxin A and nutraceuticals (butterbur).
The most urgent goal as concerns pharmaceutical innovation is the development of pathomechanism-based antimigraine drugs and personalized therapy tailored to the children and adolescents.

Keywords: antidepressants, antiepileptics, antihistamines, beta-adrenergic receptor blockers, butterbur, calcium ion channel antagonists, efficacy, migraine, onabotulinum toxin A, pediatric, prophylactic, safety, therapy, tolerability

Introduction

Migraine is a highly devastating neurovascular primary headache disorder that can affect subjects from childhood onwards [1, 2].

The Headache Classification Committee of the International Headache Society (IHS) [3] has classified migraine into subtypes: migraine without aura, migraine with aura, chronic migraine, complications of migraine, probable migraine and episodic syndromes that may be associated with migraine. The earlier name of this last subtype was childhood periodic syndromes that are commonly precursors of migraine [3]. Episodic syndromes that may be associated with migraine are further subdivided: recurrent gastrointestinal disturbance: cyclic vomiting syndrome and abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis [3]. In young patients, migraine may occur with or without aura and there may be an increased risk of the development of either of these disorders [3]. A recent retrospective study demonstrated that the prevalence of episodic syndromes that may be associated with migraine was 5.6% [4]. The most frequent types of migraine are migraine without aura and migraine with aura. The typical clinical features are a duration of 4-72 hours, a unilateral localization, a pulsating quality and moderate to severe intensity, worsening in response to routine physical activity, and usually combined with nausea, vomiting, and/or photophobia and phonophobia as concomitant symptoms of the headache [3]. In the event the occurrence of migraine aura, visual, sensory or other central nervous system symptoms develop gradually and temporarily, usually preceding the headache phase [3]. Chronic migraine, one of the devastating subtypes of migraine, has a considerable influence on the quality of life, even in young patients [5, 6]. By definition, chronic migraine is the persistence of headache for at least 15 days per month (migraine quality on at least 8 days) and for at least 3 consecutive months [3].

In pediatric migraine patients, the duration of the migraine attack may be shorter, the location of the pain is often bilateral, and abdominal pain, nausea and vomiting are more frequent [7]. The diagnosis of migraine in

children and adolescents is therefore rather difficult, and the IHS diagnostic criteria are broader than in adults [7, 8].

The importance of migraine in childhood is reflected by the fact that a majority of the headache cases observed in the pediatric emergency department involve migraine [9]. Epidemiological data have revealed that 40% of headaches are primary headaches, 75% of these cases being migraine [9]. Clinical studies have demonstrated that the prevalence of migraine increases with age, [1, 10] 3% or less in those up to 7 years old, 11% among 11 - year – olds, and 23-28% in adolescents (13-18 years old) [1, 10]. In a large cohort, of children the prevalence of migraine proved to be 10.1%, and that of migraine with aura 1.6% [11]. The prevalence of migraine depends on the age and the gender. The sex ratio of migraine patients is 1:1 (boys:girls) in childhood, the ratio subsequently increasing with the progression of age to 1:3 (males:females) [11]. The mean age of onset of migraine is 7.2 years in boys and 10.9 years in girls [1].

The pathomechanism of migraine has not been clearly elucidated, but activation and sensitization of the trigeminovascular system and distinct neuropeptides are deeply involved [12-15] (Figure 1).

In consequence of the lack of knowledge the precise pathogenesis of the initiation and the recurrence of migraine attacks, specific antimigraine prophylactic treatment is not available [16-19]. In everyday pediatric clinical practice, the recommended drugs for the prevention of migraine headache attacks are antidepressants (amitriptyline (AMI) and nortriptyline (NOR)), antiepileptics (valproates, VALPs; topiramate, TOP; levetiracetam, LEV; zonisamide, ZON; and gabapentin, GBP), antihistamines (cyproheptadine, CYP), beta-adrenergic receptor blockers (propranolol, PROP) and calcium ion channel antagonists (flunarizine, FLUN) [7, 20]. Onabotulinum toxin A (OBOT-A) has recently been applied for the alleviation of chronic migraine in children and adolescents [21-23], and butterbur may be mentioned as a nutraceutical.

This review discusses the drugs currently used in the preventive therapy of migraine in children and adolescents.

Prophylactic drug treatment in pediatric migraine

The indications of prophylactic migraine therapy include a high frequency of migraine attacks, an impairment of the quality of life and of the regularity of school attendance, the ineffective, not tolerated, contraindicated or overused acute management of headache attacks, or the presence of complex and severe accompanying symptoms or long uncomfortable aura symptoms [1, 7, 16, 17]. The fundamental aims of antimigraine treatment are a decrease of the attack frequency by at least 50% within 3 months and a diminution of the duration and intensity of the head pain [1, 17]. Although around one-third of adolescents need prophylactic antimigraine therapy, only 10-19% are offered it [24]. For this special population, the parents or other family members should be educated as to the effects and possible adverse events (AEs) of the drugs and the drug titration and dosing schedule [25]. Avoidance of the side-effects of the drugs demands slow titration (4-12 weeks) and the treatment period is suggested to be at least 6-8 weeks [25]. In general, it is very important that the pharmacological treatment of young migraine patients should be accompanied by psychological support for.

Antidepressants

Amitriptyline

AMI, a tricyclic antidepressant, has a multiple mode of action, which includes the blockade of norepinephrine and serotonin reuptake, together with anticholinergic, histaminergic and gamma-aminobutyric acid (GABA)-ergic effects [26, 27]. AMI influences the antinociceptive function via activation of the adenosine A1 receptor and enhances neuronal sensitivity to substance P (SP) [19].

In the prophylactic treatment of pediatric migraine, AMI is one of the most widely used pharmacons despite the performance of only a low number of randomized clinical trials. A recent large academic hospital study revealed that AMI was the most common preventive medication

prescribed to pediatric patients with migraine either with or without aura [28]. In a study where low-dose AMI or PROP was added to nonpharmacological therapeutic measures (e.g. relating to sleep hygiene, dietetic and lifestyle recommendations, or sun exposure), it was concluded that the both two drugs were equally effective in reducing the frequency of pediatric migraine [29]. A double-blind placebo-controlled multicenter comparative effectiveness study of AMI and TOP is ongoing (Childhood and Adolescent Migraine Prevention Study, CHAMP), with the aim of a 50% reduction in migraine frequency in children and adolescents as primary outcome [30]. The first results are planned to be published in 2016. A prospective trial has led to the finding that supplementary vitamin D therapy in addition to AMI significantly reduces the number of migraine attacks in pediatric migraine patients [31]. A randomized clinical trial focusing on the effects of cognitive behavioral therapy (CBT) plus AMI versus headache education plus AMI in chronic migraine pediatric patients proved that the reduction in the number of headache days was superior in the CBT plus AMI group [32].

The recommended dose of AMI is 10-150 mg qhs ("every night at bedtime") (at most 1 mg/kg/day) [7]. The reason for the bedtime dosing is the somnolence that occurs as one of the most common side-effects of the drug [25, 33]. Other frequent AEs are dizziness, constipation, an increased appetite and a weight gain [7]. AMI is preferred in view of its relatively favorable side effect profile and dosing regime [33]. The recommendation levels of migraine prophylactic drugs are based on the reports of the Scientific Task Force of the European Federation of Neurological Societies and the Quality Standard Subcommittee of the American Academy of Neurology and the American Headache Society [34, 35]. The recommendation level of AMI: Class IV, Level U [25] (Table 1.).

Nortriptyline

In actual medical practice instead of AMI may be replaced by NOR, which has a lower sedative effect, but mention must be made of its significant

potential cardiac side effect (arrhythmia) [7, 25]. The recommended dose of NOR is 10-75 mg qhs [7].

Antiepileptics

Valproates

The VALPs consist of valproic acid, sodium valproate and some combination of these drugs. They strongly block the peripheral and central trigeminovascular responses and nociceptive transmission, exert a great influence on the cortical neuronal hyperexcitability and suppress cortical spreading depression via the GABA-A receptor [36, 37].

A prospective randomized clinical trial in which PROP and sodium valproate were compared as concerns their efficacy in preventive migraine treatment in children and adolescents found no significant difference between these two drugs in mean headache duration per week, in headache severity, or in the complete cessation of headache attacks. The mean headache frequency per month was lower in the PROP group than in the sodium valproate group. As regards the side-effects, there was no significant difference between the two drugs [38]. Doses of 15-20 mg/kg/day appear to be effective. The common AEs of VALPs are somnolence, a skin rash, a weight gain, tremor, drowsiness, hair loss, and hematological or liver abnormalities [39, 40]. Due to their teratogenicity, VALPs cannot be recommended for females of reproductive age [19]. A recent meta-analysis focusing on the pharmacological preventive treatment of pediatric migraine indicated that VALPs were found ineffective in reducing the number of headaches per month [41]. The recommendation level of VALPs: Class IV, Level U [25].

Topiramate

As concerns migraine, TOP influences the pain transmission in the trigeminocervical complex and the third-order neurons in the ventroposteromedial thalamus [37].

A prospective clinical study concluded that a low prophylactic dose (<2 mg/kg/day) of TOP is effective in reducing the mean frequency, duration and intensity of pediatric migraine [42].

A randomized comparative clinical trial demonstrated that TOP and PROP treatment displayed the same efficiency in reducing the headache frequency and the severity and duration of migraine attacks in childhood [43].

In a further clinical study, TOP proved effective (the monthly frequency, severity and duration of migraine headache were all decreased) and safe for the prophylaxis of migraine in children [44]. A retrospective comparative trial revealed that the effects of FLUN and TOP did not differ significantly as concerns the total number of headache days per month in preadolescent and adolescent migraine patient groups with or without aura [45].

A recent review concluded that TOP is effective in decreasing the frequency of headaches in pediatric migraine patients [46]. A ≥50% reduction in migraine rate was attained in 83-95% of the patients. The recommended dose of TOP is 1-10 mg/kg/day, with a general dose of 50 mg bid (twice per day) [7]. TOP is well tolerated; its common AEs are numbness, a weight loss, a cognitive impairment (affecting the verbal fluency, concentration and working memory), fatigue, nausea and somnolence [47]. The recommendation level of TOP: Class IV, Level U [25].

Levetiracetam

LEV is a pyrolidone derivative with an antiepileptic effect. It has a novel and apparently unique mechanism of action, which may be associated with its binding to synaptic vesicle protein SV2A, therefore influencing the neurotransmitter release [48].

An early small retrospective study, on the efficacy of LEV in pediatric migraine pointed to its beneficial effect (in 10 of 19 children and adolescents, LEV eliminated the migraine headache) [49]. An open label study led to the conclusion that LEV reduced the frequency of migraine: a

more than 50% decrease in the frequency of monthly headaches and was achieved (in 18 of 20 patients), and the Pediatric Migraine Disability Assessment Test (PedMIDAS) revealed a significant decrease in disability as compared with the baseline in pediatric migraineurs [50]. The recommended daily dose of LEV is 500-1500 mg bid [7, 20]. Its safety profile appears acceptable, but its common AEs include somnolence, fatigue, irritability and dizziness [7, 20, 25]. The recommendation level of LEV: Class IV, Level U [25].

Zonisamide

ZON is a synthetic 1,2-benzisoxazole-3-methanesulfonamide, which acts by inhibiting the voltage-sensitive sodium and reducing the voltage-sensitive T-type calcium channels [51].

A very small retrospective study suggested that ZON had the capability to reduce the headache frequency in refractory pediatric headache patients (8 of 12 patients responded favorably) [52]. The recommended dose of ZON is 100-600 mg per day [7, 20]. Its common AEs are dizziness, nausea, irritability and somnolence [7, 20]. The recommendation level of ZON: Class IV, Level U [25].

Gabapentin

GBP is structurally related to GABA, but without any direct effects on GABA or any of its receptors [53]. There have been only very rare clinical studies of GBP in pediatric migraine. Belman et al. reported data on 18 migraine children treated with GBP, 80% of whom attained a more than 50% reduction in migraine frequency [20, 54]. The recommended dose of GBP is 300-1200 mg three times daily (tid) [20]. The common AEs of GBP are sedation, ataxia, fatigue and peripheral edema [20]. The recommendation level of GBP: Class IV, Level U [25].

Antihistamines

Cyproheptadine

CYP exerts antihistaminergic, antiserotoninergic and anticholinergic actions, and has the ability to block (competitively and reversibly antagonize) the histamine and serotonin receptors [55]. The 5-hydroxytryptamine 1B and 1D receptors take part in the activation of the trigeminovascular system via cerebrovascular vasoconstriction and inhibition of the release of vasoactive neuropetides, e.g. calcitonin gene-related peptide (CGRP), SP and pituitary adenylate cyclase-activating polypeptide (PACAP) [2, 18, 56, 57].

In a double-blind controlled study in which patients aged 16 to 53 years (mean 28.6) received CYP as prophylactic treatment of migraine, the mean headache frequency decreased from 8.4 to 3.7 per month, with an overall positive response rate of 83% [58]. A recent retrospective clinical study led to the finding that CYP was effective in abdominal migraine and in cyclic vomiting syndrome (among the functional gastrointestinal disorders), the responder rate proving to be high: in abdominal migraine 13 of 18 pediatric patients (72%) and in cyclic vomiting syndrome 6 of 8 patients (75%) exhibited a clinical improvement [59]. CYP is available as tablets and liquid suspensions, with recommended doses of 0.25-1.5 mg/kg/day [20]. The most common side-effects of CYP are sleepiness, a weight gain and an increased appetite [7, 33, 59]. An investigation by a large academic children's hospital of the prescription patterns in patients aged 2-17 years demonstrated, that the one of the most common by prescribed medications for pediatric migraine prophylaxis was CYP [28]. The recommendation level of CYP: Class IV, Level U [25].

Beta-adrenergic receptor blockers

Propranolol

PROP, a nonselective beta-adrenergic receptor blocker that inhibits the third-order trigeminovascular nociceptive neurons in the ventroposteromedial nucleus of the thalamus [19, 60], has a long history

of use in migraine prophylaxis in children [61]. The results emerging from clinical trials have been conflicting [1, 25].

In recent studies, PROP has been widely used as a comparative pharmacon.

In a prospective randomized trial which compared the prophylactic anti-migraine effects of PROP an VALP in children (aged 5-15 years) with migraine without aura, VALP was found to be superior to PROP only in reducing the mean headache frequency per month [38]. Low-dose PROP and low-dose AMI proved equally effective in reducing the frequency of severe migraine attacks in pediatric migraineurs (mean age 12.54 years), but it was noteworthy that PROP had fewer side-effects [29]. A randomized clinical comparative trial relating to childhood migraine prophylaxis revealed that TOP and PROP displayed the same efficacy in reducing the frequency, severity and duration of migraine attacks [43]. In contrast, another parallel single-blinded randomized clinical trial involving 5-15-year-old migraineurs revealed that TOP was more effective than PROP in reducing the monthly frequency, severity and duration of headache and in the PedMIDAS score. Both drugs exerted transient and mild side-effects [62]. A recent comparative randomized controlled trial that focused on the effects of PROP as compared with pregabalin in pediatric migraine led to the result that pregabalin reduced the headache frequency considerably more effectively than did PROP [63].

The recommended dose of PROP is 2-4 mg/kg/day. The most common side-effects are hypotension, depression and dizziness [7, 20]. The unfavorable AEs of PROP have limited its wide-ranging use in young migraineurs [25]. The recommendation level of PROP: Class II, Level U [25].

Calcium ion channel antagonists

Flunarizine

FLUN is a nonselective calcium ion entry blocker that mainly acts via T-type ion channels [64]. Its exact mechanism of action in migraine is still

unknown, but it may involve smooth muscle inhibition in the vasculature and effects on neuronal activation via 5-hydroxytryptamine antagonism [65].

A classical double-blind, placebo-controlled, crossover study revealed that FLUN was effective in the prophylaxis of childhood migraine [66].

A single-center retrospective observational study which evaluated the effects of FLUN in various subtypes of childhood migraine, i.e. migraine without aura, migraine with aura, sporadic and familial hemiplegic migraine, found that FLUN was more effective in the hemiplegic migraine group [67].

With the focus on disability and the quality of life of pediatric migraineurs, FLUN treatment significantly decreased the PedMIDAS score, but in the same study, FLUN was inferior to TOP and PROP in the PedMIDAS system [68].

The recommended dose of FLUN is 5-10 mg qhs [7, 20]. The common AEs of FLUN are sedation, a weight gain, fatigue and gastrointestinal discomfort [7, 20, 25].

The recommendation level of FLUN: Class I, Level B [25].

Onabotulinum toxin A

One of the latest therapeutic regimes for adult migraine patients is OBOT-A injection treatment, which was approved by the US Food and Drug Administration in 2010 [69, 70].

Botulinum neurotoxin-A is a purified neurotoxin complex produced by the anaerobic bacterium *Clostridium botulinum [71, 72].* The main mechanism of action of botulinum toxin involves the targeting of the neuromuscular junctions by means of a specific cleavage of the soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein receptor complex (SNARE)-like synaptosomal-associated protein of 25 kDa (SNAP-25) [71, 72]. The final outcome of this multistage process is the breaking of pain neurotransmission, including the inhibition of the release of migraine-related neuropeptides (e.g. CGRP and SP) and glutamate [71-74].

The prevalence of chronic migraine among pediatric migraineurs is around 3% [23]. A retrospective case series study of the use of OBOT-A for the treatment of refractory pediatric chronic daily headache, including chronic migraine, revealed that 4 of 10 patients reported a decrease in headache intensity and 2 of them decrease in headache frequency, and these 4 responder patients achieved a favorable improvement of the quality of life [21]. A retrospective review of the data on 45 pediatric chronic daily headache patients who participated in 252 OBOT-A injections (average dose 188.5 ± 32 units) concluded that the monthly headache frequency was decreased and the PedMIDAS score showed an improvement [23]. A recent small case series study of chronic migraineurs (aged 13-17 years) showed a good responder rate (7 of 10 patients). The number of headache days per month decreased from 19.2 to 10.1 [22]. The recommended dose of OBOT-A is 100 units. The common AEs of OBOT-A are redness or temporary pain at the injection site, ptosis and blurred vision [25]. The recommendation level of OBOT-A: Class IV, Level U [25].

Nutraceuticals (Herbal products)

Petasites hybridus (butterbur)

Extracts of the roots of *Petasites hybridus* exert an anti-inflammatory effect via the inhibition of leukotriene production, and influence intracellular calcium accumulation through the L-type voltage-gated calcium ion channels [75].

A multicenter prospective open-label study with a butterbur root extract for migraine prevention (50-150 mg for 4 months), which involved 108 children and adolescents (aged 6-17 years) resulted in 77% of all patients reporting a 63% decrease in frequency of migraine attacks [76]. A prospective, randomized, partly double-blind, placebo-controlled, parallel-group trial was set up to examine the prophylactic antimigraine effects of butterbur root extract and music therapy in primary school children [77]. The evaluation of this study revealed that both the butterbur extract and music therapy were superior to placebo in reducing the frequency of

headache attacks in the follow-up period [77]. The recommended dosage of butterbur is 50-150 mg per day. The main AE of butterbur extract is burping. The recommendation level of *Petasites* : Class II, Level U [25].

Conclusion

The pathomechanism of migraine is not fully understood, and personalized therapy tailored to the patient is therefore not available for pediatric migraine. A further difficulty is the fact that the latest therapeutic guidelines were published more than ten years ago. This review has surveyed the latest literature data relating to the prophylactic drugs used in the daily clinical practice in children and adolescents with migraine. For the near future, basic experimental and human headache research is needed, such as innovative pharmaceutical investments with fully humanized monoclonal antibodies against CGRP and CGRP receptors. Randomized clinical trials are still necessary as regards currently used prophylactic antimigraine drugs and new compounds designed for the treatment of young migraineurs. Overall, new therapeutic guidelines are clearly required in this field.

Conflict of interest

The authors declare that they have no conflict of interest and have received no payment in the preparation of their manuscript.

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References

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1. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004;63:2215-24.
**2. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol. 2013;75:365-91.
An excellent review of the pathomechanism of migraine.
3. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629-808.
4. Teixeira KC, Montenegro MA, Guerreiro MM. Migraine equivalents in childhood. J Child Neurol. 2014;29:1366-9.
5. Bigal ME, Lipton RB, Tepper SJ, Rapoport AM, Sheftell FD. Primary chronic daily headache and its subtypes in adolescents and adults. Neurology. 2004;63:843-7.
6. Ernst MM, O'Brien HL, Powers SW. Cognitive-behavioral therapy: how medical providers can increase patient and family openness and access to evidence-based multimodal therapy for pediatric migraine. Headache. 2015.
*7. Kacperski J, Hershey AD. Preventive drugs in childhood and adolescent migraine. Curr Pain Headache Rep. 2014;18:422.
Novel findings concerning the potential options of the preventive treatment of pediatric migraine.
8. Barnes NP. Migraine headache in children. BMJ Clin Evid. 2015;2015.
9. Sheridan DC, Spiro DM, Meckler GD. Pediatric migraine: abortive management in the emergency department. Headache. 2014;54:235-45.
10. Oakley CB, Kossoff EH. Migraine and epilepsy in the pediatric population. Curr Pain Headache Rep. 2014;18:402.
11. Merikangas KR. Contributions of epidemiology to our understanding of migraine. Headache. 2013;53:230-46.
12. Edvinsson L, Villalon CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. Pharmacol Ther. 2012;136:319-33.
13. Tajti J, Pardutz A, Vamos E, Tuka B, Kuris A, Bohar Z et al. Migraine is a neuronal disease. J Neural Transm. 2011;118:511-24.
14. Varga H, Pardutz A, Tajti J, Vecsei L, Schoenen J. [The modulatory effect of estrogen on the caudal trigeminal nucleus of the rat in an animal model of migraine]. Ideggyogy Sz. 2006;59:389-95.
15. Vecsei L, Tuka B, Tajti J. Role of PACAP in migraine headaches. Brain. 2014;137:650-1.
16. Evers S. Treatment of migraine with prophylactic drugs. Expert Opin Pharmacother. 2008;9:2565-73.
17. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009;16:968-81.
18. Tajti J, Szok D, Majlath Z, Tuka B, Csati A, Vecsei L. Migraine and neuropeptides. Neuropeptides. 2015;52:19-30.

19. Vecsei L, Majlath Z, Szok D, Csati A, Tajti J. Drug safety and tolerability in prophylactic migraine treatment. Expert Opin Drug Saf. 2015;14:667-81.
**20. Kacperski J. Prophylaxis of migraine in children and adolescents. Paediatr Drugs. 2015;17:217-26.
A paper summarizing all of the important aspects of the prophylactic drug treatment of children and adolescents.
21. Ahmed K, Oas KH, Mack KJ, Garza I. Experience with botulinum toxin type A in medically intractable pediatric chronic daily headache. Pediatr Neurol. 2010;43:316-9.
22. Bernhard MK, Bertsche A, Syrbe S, Weise S, Merkenschlager A. Botulinum toxin injections for chronic migraine in adolescents - an early therapeutic option in the transition from neuropaediatrics to neurology. Fortschr Neurol Psychiatr. 2014;82:39-42.
23. Kabbouche M, O'Brien H, Hershey AD. OnabotulinumtoxinA in pediatric chronic daily headache. Curr Neurol Neurosci Rep. 2012;12:114-7.
24. Lewis DW, Diamond S, Scott D, Jones V. Prophylactic treatment of pediatric migraine. Headache. 2004;44:230-7.
**25. O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of pediatric migraine. Curr Treat Options Neurol. 2015;17:326.
The paper gives an updated overview of the treatment of pediatric migraine.
26. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol. 2012;52:6-17.
27. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. Cephalalgia. 2002;22:491-512.
28. Johnson A, Bickel J, Lebel A. Pediatric migraine prescription patterns at a large academic hospital. Pediatr Neurol. 2014;51:706-12.
29. Eidlitz-Markus T, Dlugatch Y, Haimi-Cohen Y, Goldberg-Stern H, Zeharia A. Nonpharmacologic treatment of migraine with low-dose propranolol or amitriptyline. Pediatr Neurol. 2012;46:345-9.
30. Hershey AD, Powers SW, Coffey CS, Eklund DD, Chamberlin LA, Korbee LL et al. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. Headache. 2013;53:799-816.
31. Cayir A, Turan MI, Tan H. Effect of vitamin D therapy in addition to amitriptyline on migraine attacks in pediatric patients. Braz J Med Biol Res. 2014;47:349-54.
32. Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA. 2013;310:2622-30.
33. O'Brien HL, Kabbouche MA, Hershey AD. Treating pediatric migraine: an expert opinion. Expert Opin Pharmacother. 2012;13:959-66.
34. Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, Bassetti CL et al. Guidance for the preparation of neurological management guidelines

by EFNS scientific task forces - revised recommendations 2012. Eur J Neurol. 2013;20:410-9.
35. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1337-45.
36. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol. 2006;59:652-61.
37. Hoffmann J, Akerman S, Goadsby PJ. Efficacy and mechanism of anticonvulsant drugs in migraine. Expert Rev Clin Pharmacol. 2014;7:191-201.
38. Bidabadi E, Mashouf M. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatr Drugs. 2010;12:269-75.
39. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. Lancet Neurol. 2010;9:285-98.
40. Shahien R, Beiruti K. Preventive agents for migraine: focus on the antiepileptic drugs. J Cent Nerv Syst Dis. 2012;4:37-49.
41. El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatr. 2013;167:250-8.
42. Abbaskhanian A, Sadeghi HR, Erfani A, Rezai MS. Effective dose of topiramate in pediatric migraine prophylaxis. J Pediatr Neurosci. 2012;7:171-4.
43. Tonekaboni SH, Ghazavi A, Fayyazi A, Khajeh A, Taghdiri MM, Abdollah Gorji F et al. Prophylaxis of childhood migraine: topiramate versus propranolol. Iran J Child Neurol. 2013;7:9-14.
44. Fallah R, Akhavan Karbasi S, Shajari A, Fromandi M. The efficacy and safety of topiramate for prophylaxis of migraine in children. Iran J Child Neurol. 2013;7:7-11.
45. Kim H, Byun SH, Kim JS, Lim BC, Chae JH, Choi J et al. Comparison of flunarizine and topiramate for the prophylaxis of pediatric migraines. Eur J Paediatr Neurol. 2013;17:45-9.
46. Deaton TL, Mauro LS. Topiramate for migraine prophylaxis in pediatric patients. Ann Pharmacother. 2014;48:638-43.
47. Fritz N, Glogau S, Hoffmann J, Rademacher M, Elger CE, Helmstaedter C. Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy. Epilepsy Behav. 2005;6:373-81.
48. Wright C, Downing J, Mungall D, Khan O, Williams A, Fonkem E et al. Clinical pharmacology and pharmacokinetics of levetiracetam. Front Neurol. 2013;4:192.
49. Miller GS. Efficacy and safety of levetiracetam in pediatric migraine. Headache. 2004;44:238-43.
50. Pakalnis A, Kring D, Meier L. Levetiracetam prophylaxis in pediatric migraine--an open-label study. Headache. 2007;47:427-30.
51. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. Seizure. 2004;13(Suppl 1):S5-9; discussion S10.

52. Pakalnis A, Kring D. Zonisamide prophylaxis in refractory pediatric headache. Headache. 2006;46:804-7.
53. Moshe SL. Mechanisms of action of anticonvulsant agents. Neurology. 2000;55:S32-40; discussion S54-8.
54. Belman AL, Milazo M, Savatic M. Gabapentin for migraine prophylaxis in children. Ann Neurol. 2001;50(Suppl 1):S109.
55. Okuma H, Iijima K, Yasuda T, Tokuoka K, Kitagawa Y. Preventive effect of cyproheptadine hydrochloride in refractory patients with frequent migraine. Springerplus. 2013;2:573.
56. Tajti J, Tuka B, Botz B, Helyes Z, Vecsei L. Role of pituitary adenylate cyclase-activating polypeptide in nociception and migraine. CNS Neurol Disord Drug Targets. 2015;14:540-53.
57. Tuka B, Helyes Z, Markovics A, Bagoly T, Szolcsanyi J, Szabo N et al. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. Cephalalgia. 2013;33:1085-95.
58. Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurol India. 2000;48:223-6.
59. Madani S, Cortes O, Thomas R. Cyproheptadine use in children with functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr. 2015.
60. Shields KG, Goadsby PJ. Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: a role in migraine? Brain. 2005;128:86-97.
61. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. Acta Neurol Scand. 1974;50:109-15.
62. Fallah R, Divanizadeh MS, Karimi M, Mirouliaei M, Shamszadeh A. Topiramate and propranolol for prophylaxis of migraine. Indian J Pediatr. 2013;80:920-4.
63. Bakhshandeh Bali M, Rahbarimanesh AA, Sadeghi M, Sedighi M, Karimzadeh P, Ghofrani M. Comparison of propranolol and pregabalin for prophylaxis of childhood migraine: a randomised controlled trial. Acta Med Iran. 2015;53:276-80.
64. Della Paschoa OE, Hoogerkamp A, Edelbroek PM, Voskuyl RA, Danhof M. Pharmacokinetic-pharmacodynamic correlation of lamotrigine, flunarizine, loreclezole, CGP40116 and CGP39551 in the cortical stimulation model. Epilepsy Res. 2000;40:41-52.
65. Abu-Arafeh I. Flunarizine for the prevention of migraine - a new look at an old drug. Dev Med Child Neurol. 2012;54:204-5.
66. Sorge F, De Simone R, Marano E, Nolano M, Orefice G, Carrieri P. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. Cephalalgia. 1988;8:1-6.
67. Peer Mohamed B, Goadsby PJ, Prabhakar P. Safety and efficacy of flunarizine in childhood migraine: 11 years' experience, with emphasis on its effect in hemiplegic migraine. Dev Med Child Neurol. 2012;54:274-7.
68. Topcu Y, Hiz Kurul S, Bayram E, Sozmen K, Yis U. The Paediatric migraine disability assessment score is a useful tool for evaluating prophylactic migraine treatment. Acta Paediatr. 2014;103:e484-9.
69. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB et al. OnabotulinumtoxinA for treatment of chronic migraine:

pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50:921-36.
70. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331:48-56.
71. Frampton JE. OnabotulinumtoxinA (BOTOX(R)): a review of its use in the prophylaxis of headaches in adults with chronic migraine. Drugs. 2012;72:825-45.
72. Turton K, Chaddock JA, Acharya KR. Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. Trends Biochem Sci. 2002;27:552-8.
73. Szok D, Csati A, Vecsei L, Tajti J. Treatment of chronic migraine with onabotulinumtoxinA: mode of action, efficacy and safety. Toxins (Basel). 2015;7:2659-73.
74. Tajti J, Szok D, Tuka B, Csati A, Kuris A, Majlath Z et al. Botulinum neurotoxin-a therapy in migraine. Ideggyogy Sz. 2012;65:77-82.
75. Orr SL, Venkateswaran S. Nutraceuticals in the prophylaxis of pediatric migraine: Evidence-based review and recommendations. Cephalalgia. 2014;34:568-83.
76. Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. Headache. 2005;45:196-203.
77. Oelkers-Ax R, Leins A, Parzer P, Hillecke T, Bolay HV, Fischer J et al. Butterbur root extract and music therapy in the prevention of childhood migraine: an explorative study. Eur J Pain. 2008;12:301-13.
78. Tajti J, Csati A, Vecsei L. Novel strategies for the treatment of migraine attacks via the CGRP, serotonin, dopamine, PAC1, and NMDA receptors. Expert Opin Drug Metab Toxicol. 2014;10:1509-20.

Table

Table 1 Prophylactic drugs recommended in pediatric migraine

Drugs	Recommended daily dosage	Common adverse events	Recommendation level
Antidepressants			
Amitriptyline	10-150 mg qhs	dizziness, constipation, increased appetite, weight gain	Class IV Level U
Nortriptyline	10-75 mg qhs	cardiac (arrhythmia)	no data
Antiepileptics			
Valproates	15-20 mg/kg/day	somnolence, skin rash, weight gain, tremor, drowsiness, hair loss, hematological or liver abnormalities	Class IV Level U
Topiramate	1-10 mg/kg/day	numbness, weight loss, cognitive impairment, fatigue, nausea, somnolence	Class IV Level U
Levetiracetam	500-1500 mg bid	somnolence, fatigue, irritability, dizziness	Class IV Level U
Zonisamide	100-600 mg/day	dizziness, nausea, irritability, somnolence	Class IV Level U
Gabapentin	300-1200 mg tid	sedation, ataxia, fatigue, peripheral edema	Class IV Level U
Antihistamines			
Cyproheptadine	0.25-1.5 mg/kg/day	sleepiness, weight gain, increased appetite	Class IV Level U
Beta-adrenergic receptor blockers			
Propranolol	2-4 mg/kg/day	hypotension, depression, dizziness	Class II Level U
Calcium ion channel antagonists			
Flunarizine	5-10 mg qhs	sedation, weight gain, fatigue, gastrointestinal discomfort	Class I Level B
Onabotulinum toxin A	100 units	redness or temporary pain at	Class IV Level U

		the injection site, ptosis, blurred vision	
Nutraceuticals (herbal products)			
Petasites hybridus (butterbur)	50-150 mg/day	burping	Class II Level U

Abbreviations: qhs: every night at bedtime; bid: twice daily; tid: three times daily
Modified from Ref. [7, 20, 25].

Figure legends

Figure 1 Scheme of the activation of the trigeminovascular system

The putative mechanism of activation of the sensitization of the trigeminovascular system is the following. The process of cortical spreading depression (CSD), a slowly propagating wave of neuronal and glial depolarization, activates trigeminal nociceptors. Activation of meningeal afferents leads to the release of CGRP, SP, and PACAP via the peripheral branch of the trigeminal pseudounipolar neurons. The released substances may promote neurogenic inflammation in the cerebral dura mater and lead to activation and sensitization of peripheral meningeal nerve terminals, the nociceptors. The consequences of peripheral sensitization include the central sensitization of the second-order neurons in the trigeminocervical complex (TCC) as well as that of the third-order neurons in the thalamus.
Modified from Ref. [2, 78].

Abbreviations: CGRP: calcitonin gene-related peptide; CSD: cortical spreading depression; PACAP: pituitary adenylate cyclase-activating polypeptide; SP: substance P; TCC: trigeminocervical complex; TRIG: trigeminal ganglion.