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Headache (JR Couch, Section Editor)

Other Preventive Anti-Migraine Treatments: ACE Inhibitors, ARBs, Calcium Channel Blockers, Serotonin Antagonists, and NMDA Receptor Antagonists

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Abstract

Purpose of review Migraine causes more years of life lived with disability than almost any other condition in the world and can significantly impact the lives of individuals with migraine, their families, and society. The use of medication for the prevention of migraine is an integral component to reducing disability caused by migraine. There are many different drug classes that have been investigated and shown efficacy in migraine prophylaxis. This article examines several of the classes of medications that are used for migraine preventive treatment, specifically, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, serotonin antagonists, alpha-adrenergic agonists, and N-methyl-D-aspartic acid receptor antagonists.

Recent findings There have been randomized control trials investigating medications in these drug classes since the most recent guidelines for migraine prevention in adults were published by the American Academy of Neurology, American Headache Society, and the Canadian Headache Society. In these investigations, enalapril, candesartan, and memantine all demonstrated efficacy for migraine prevention. The evidence for these and the aforementioned drug classes are reviewed.

Summary When oral medications are being selected for migraine prevention, comorbid and coexistent medical conditions, concomitant medications, patient preference, and

pregnancy and breast-feeding plans should be considered. Within the drug classes discussed, memantine and candesartan have a moderate level of evidence for efficacy.

Introduction

Migraine affects approximately 12% of the US adult population [1]. Globally, it represents the second highest number of years lived with disability (YLD) by the World Health Organization in the Global Burden of Disease Study which estimated that migraine is responsible for over 45 million YLD [2]. The disability caused by migraine comes at considerable cost to the individual and their families in the form of physical distress, emotional distress, and financial burden. It also imposes a burden on society with regard to health care and productivity costs [3]. Therefore, effective strategies for migraine prevention are of utmost importance.

An expert panel from the American Migraine Prevalence and Prevention (AMPP) Study developed recommendations for the use of preventive treatment [4] based on migraine frequency and impairment with the inability to function considered as severe impairment:

1. Prevention should be *offered* to people with migraine reporting either 6 or more headache days per month, 4 or more headache days with at least some impairment, or 3 or more headache days with severe impairment or requiring bed rest.
2. Prevention should be *considered* for people with migraine who experience 4 or 5 migraine days per month with normal functioning, 3 migraine days with some impairment, or 2 migraine days with severe impairment.

Using these recommendations, it was estimated that 38% of adults with migraine should be on migraine prevention. However, only 12% of those with migraine in the USA were found to be using preventive migraine treatment [4].

In addition to pharmacological treatment for migraine prevention, education, lifestyle, and behavioral management are important for the overall management of patients. Cognitive behavioral therapy, biofeedback, relaxation training, and physical therapy have all been shown to be beneficial [5, 6]. Optimization of lifestyle including dietary modification, exercise, stress reduction, sleep hygiene, and trigger avoidance can reduce migraine burden and improve quality of life [7•]. While such discourse may seem problematic under the time constraints of patient visits, even brief interventions have been demonstrated to be effective for even the most difficult of migraine conditions, chronic migraine, and medication-overuse headache [8, 9]. Finally, combining non-pharmacological and pharmacological treatment enhances efficacy and adherence to both and leads to more sustained positive outcomes [10•]. There are also several neurostimulation devices with demonstrated efficacy for migraine prevention ([11•]).

Guidelines for prevention of episodic migraine in adults

The American Association of Neurology (AAN) and American Headache Society (AHS) have developed joint evidence-based guidelines for the oral pharmacologic prevention of migraine in adults (updated in 2012) [12••], as well as for the use of onabotulinumtoxinA [13]. Additionally, the Canadian Headache Society (CHS) produced guidelines for migraine prevention in adults in 2012 [14••]. Each of pharmacologic classes mentioned in these guidelines will be discussed in this issue of *Current Treatment Options in Neurology*. This particular review will address alpha-adrenergic agonists, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and serotonin antagonists as preventive migraine agents in

Table 1. Evaluation of the research studies and 2012 AAN-AHS and CHS guideline recommendations for the use of certain pharmaceuticals for migraine prevention in adults

Medication and class	AAN Episodic Migraine Guidelines (2012 Update)	Canadian Headache Society Guidelines (2012)	Additional evidence*
ACEIs			
Captopril	Not evaluated	Not evaluated	1 poor quality, Class III, study in 1992 showed efficacy, but had a high frequency of intolerable side effects [18].
Enalapril	Not evaluated	Not evaluated	1 fair quality, Class II study, in 2013 showed efficacy and reported only transient, mild side effects [16•].
Lisinopril	Level C. [19]	Weak recommendation for use. Low level of evidence [19]	No additional evidence
ARBs			
Candesartan	Level C. [20]	Strong recommendation for use. Moderate level of evidence. [20]	1 fair quality, Class II study in 2014 showed superior efficacy over placebo and comparable efficacy to propranolol. Side effects were more significant than placebo [15].
Telmisartan	Level C negative [21]	Evidence considered poor. No recommendation made. [21]	No additional evidence
Alpha adrenergic agonists			
Clonidine	Level C. [22–38]	Not recommended based on expert opinion; no evaluation of studies.	No additional evidence
Guanfacine	Level C. [39]	Not evaluated	No additional evidence.
Tizanidine	No mention	No mention	1 fair quality, Class II, study in 2001 using patients with chronic daily headache of which 77% had chronic migraine showed efficacy with high frequency of side effects. [40]
CCBs			
Nicardipine	Level U. [41]	Not evaluated	No additional evidence
Nifedipine	Level U. [42–46]	Not evaluated	No additional evidence
Nimodipine	Level U. [47–56]	Not evaluated	No additional evidence
Verapamil	Level U. [57–59]	Weak recommendation for use. Low level of evidence. [57, 58]	No additional evidence
Flunarizine	Not available in the USA		No additional evidence

Table 1. (Continued)

Medication and class	AAN Episodic Migraine Guidelines (2012 Update)	Canadian Headache Society Guidelines (2012)	Additional evidence*
		Weak recommendation for use. High level of evidence. [60–68]	
NMDAR antagonists			
Memantine	No mention	Not evaluated	1 good quality, Class 1, study showed efficacy and had a low side-effect profile.
Serotonin antagonists			
Cyproheptadine	Level C [69]	Not evaluated	No additional evidence
Pizotifen	Not available in the USA	Weak recommendation for use High level of evidence. [70–74]	No additional evidence

Level C, weak evidence. Possibly effective and may be considered for migraine prevention
Level U, evidence is inadequate or conflicting to support or refute the use for migraine prevention
*Only double-blind randomized, placebo-controlled trials in adults were considered

adults. In addition, N-methyl-D-aspartic acid receptor (NMDAR) antagonists will be briefly discussed. Only medications that are available in the USA and Canada have been included.

Newer evidence

Since the 2012 AAN-AHS and CHS guidelines, there have been few double-blind randomized control trials (RCT) examining pharmaceuticals for migraine prevention in the classes of medications covered in this article. Precisely, there has been one additional study each involving candesartan [15•] and enalapril [16•], and the first RCT of an NMDAR antagonist, memantine [17•].

None of the medications in the drug classes reviewed in this paper was considered to have higher than level C (weak) evidence by the current AAN-AHS guidelines (Table 1), and the current CHS guidelines only give strong recommendation (with moderate level of evidence) to candesartan. Despite having had only moderate level of evidence, it was given strong recommendation because of the paucity of side effects (Table 1). Both sets of guidelines are currently in the process of being updated.

Mechanism of action of migraine preventive medications

Migraine is a complex paroxysmal disorder of sensory and pain processing that is not yet fully understood [75•]. Genetic, biologic, and environmental influences allow for activation of the trigeminal cervical complex which ultimately disrupts cortical and brainstem excitatory-inhibitory balance, particularly in sensory and pain pathways, resulting in heightened sensitivity to sensory stimuli and sensitization of central trigeminal pain pathways. Release of nociceptive and vasoactive peptides such as calcitonin gene -related peptide (CGRP) and pituitary adenylate cyclase-activated peptide (PACAP) appeared to be integrally involved in the pathogenesis of the symptoms of migraine. Recently, monoclonal antibodies against CGRP and its receptor and small molecule CGRP receptor antagonists have been demonstrated to be effective for the prevention of migraine [76•], while monoclonal antibodies against PACAP receptors are in development [77] (ClinicalTrials.gov Identifier: NCT03238781). Likely, based on genetic factors, some are also predisposed to the development of cortical spreading depression resulting in the reversible neurological symptoms of the migraine aura. Multiple drugs and devices that prevent migraine, with and without aura, have been shown in preclinical animal models to disrupt or prevent cortical spreading depression [78].

Alpha-adrenergic agonists

There is no conclusive evidence that alpha-adrenergic agonists are efficacious in migraine prevention, although there are several possible mechanisms of action. Alpha-adrenergic agonists stimulate several different subtypes of receptors that are present throughout the central and peripheral nervous system [79]. In the periphery, they can act at pre-synaptic terminals and inhibit the release of norepinephrine from the sympathetic nerves resulting in decreases in sympathetic tone and modulation of vasodilation/constriction [80]. This was once the presumed mechanism for migraine prevention. Additionally, activation of

alpha-adrenergic receptors can inhibit calcium ion currents and mediate analgesia in the spinal cord [81, 82].

ACEIs and ARBs

ACEIs and ARBs are presumed to have a similar mechanism of action. Recent preclinical studies suggest that there is a tissue-based renin-angiotensin system present in the brain and that this system plays a role in the relay of nociceptive signals, neurogenic inflammation, endothelial dysfunction, and oxidative stress [83]. While not confirmed yet in humans, it is hypothesized that these factors may play a role in the pathogenesis of migraine.

CCBs

CCBs have mixed results with regard to their efficacy for migraine prevention and a mechanism of action for the class has not been established. Calcium channels are found throughout the central and peripheral nervous system and play a role in neurotransmission and inhibitory-excitatory balance [84, 85]. There are different subtypes of calcium channels and isoforms of subunits of the channels which have different properties and serve different physiologic functions. In particular, mutations in the gene that encodes a subunit of the voltage-gated P/Q-type calcium channel is responsible for familial hemiplegic migraine (FHM) type 1 [86] and while there have been no randomized control trials of preventive treatments for FHM, several case series have reported some measure of efficacy for calcium channel antagonists [87].

Flunarizine is a non-selective calcium channel blocker and an antagonist of voltage-gated calcium channels with substantially less effect on blood pressure than the other CCBs. It also has dopamine antagonist properties with D2 receptor specificity [88] which may contribute to its efficacy in migraine prevention. While the role of the dopaminergic system is not fully understood in migraine, dopamine antagonists are often used in the acute treatment of migraine [89]. In addition, alterations in release of dopamine occur during migraine attacks [90] and patients taking flunarizine had reduced D2 receptor-binding affinity than compared to controls [91].

NMDAR antagonists

The NMDAR is a glutamatergic receptor present on neurons in the central and peripheral nervous system. Glutamate is an amino acid and excitatory neurotransmitter that binds to NMDARs. It is present at higher levels in the cerebrospinal fluid of people with migraine compared to individuals without migraine [92] and has also been found to be elevated during migraine attacks [93]. In animal experiments, glutamate induces cortical spreading depression [94] and is associated with trigeminal activation and the development of central sensitization in a migraine model [95]. Glutamate is implicated in central sensitization and the progression of migraine [96, 97]. Thus, blockade of glutamate receptors is a target for migraine prevention and the proposed mechanism of action of memantine.

Serotonin antagonists

Serotonin activates peripheral afferent sensory nerves and the binding of serotonin to its 5-HT3 receptor causes the release of CGRP [98]. Therefore, serotonin

Table 2. Evaluation and use of certain pharmaceuticals for prevention of migraine in adults

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
ACEIs				
Captopril MWOA 20/26 Class III [18]	Significant reduction compared with placebo at 4 months in combined measure of attack number, duration, and severity.	*Micromedex* Common: hypotension, rash, hyperkalemia, altered taste, cough. Serious: Stevens-Johnson syndrome, intestinal angioedema, agranulocytosis, neutropenia, angioedema, anaphylactoid reaction. *Migraine study*: Cough, rash. PSC: D BF: infant risk is minimal.	Contraindicated in hereditary or idiopathic angioedema. Do not use simultaneously with ARBs or direct renin inhibitor (aliskiren). May cause hyperkalemia when used with drugs/supplements that increase potassium. Use caution in patients with renal artery stenosis, chronic kidney disease, CHF. *Monitor*:	25 mg daily × 7 days then, 25 mg BID × 7 days then, 25 mg TID. Consider in patients with hypertension, diabetic nephropathy and/or kidney disease and/or history of MI and/or heart failure not already on an ACEI or ARB, or switching from current ACEI or ARB if not effective for migraine.
Enalopril MWOA 40/40 Class II [16•]	Significant reduction compared with placebo at 1 and 2 months in the number, severity and duration of attacks per month.	*Micromedex* Common: hyperkalemia, dizziness, elevated BUN/Cr. Serious: Hypotension, intestinal angioedema, agranulocytosis, hepatotoxicity, liver failure, acute renal failure/impairment, angioedema, anaphylactoid reaction. *Migraine study*: cough 3/12. PSC: X BF: infant risk is minimal.	- BP during titration and periodically. - Periodic electrolytes and renal function - WBC counts in patients with renal disease or collagen vascular disease, periodically	5 mg daily × 7 days then, 10 mg daily Consider in patients with hypertension, diabetic nephropathy and/or kidney disease and/or history of MI and/or heart failure not already on an ACEI or ARB, or switching from current ACEI or ARB if not effective for migraine.
Lisinopril MWOA MWA 47/60 Class II [19]	Significant reduction in hours and days with headache, and days with migraine.	*Micromedex* Common: hypotension, chest pain, syncope, dizziness, headache, cough. Serious: severe hypotension, Stevens-Johnson syndrome, toxic		10 mg daily × 7 days then, 20 mg daily. Consider in patients with hypertension, diabetic nephropathy and/or kidney disease and/or history of MI

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
		epidermal necrolysis, hyperkalemia, intestinal angioedema, acute renal failure/renal impairment. Angioedema of the head and/or neck. Anaphylaxis. *Migraine study*: cough 8/60. Dizziness 7/60. Syncope/presyncope 3/60. PSC: X BF: infant risk cannot be ruled out.		and/or heart failure not already on an ACEI or ARB, or switching from current ACEI or ARB if not effective for migraine.
ARBs				
Candesartan MWOA MWA 46/60 Class II [20] MWOA MWA 54/72 Class II [15•]	Significant reduction compared to placebo after 12 weeks in number of headache days as well as many secondary endpoints in both studies.	*Micromedex* Common: hypotension, backache, dizziness, pharyngitis, rhinitis, URI Serious: none reported Migraine studies: dizziness, tiredness, paresthesias PSC: D BF: infant risk cannot be ruled out.	Contraindicated in hereditary or idiopathic angioedema Do not use simultaneously with ACEIs or direct renin inhibitor (aliskiren). May cause hyperkalemia when used with drugs/supplements that increase potassium Use caution in patients with renal artery stenosis, chronic kidney disease, CHF. *Monitor*: - BP during titration and periodically. - Periodic renal function and electrolytes in patients taking NSAIDs or other drugs that affect the rennin-angiotensin system (e.g., NSAIDS).	4 mg daily. Increase by 4 mg every 3–5 days to 16 mg daily. Max 32 mg daily Consider in patients with hypertension not already on an ACEI or ARB, or switching from current ACEI or ARB if not effective for migraine.
Telmisartan MWOA MWA 84/95 Class II [21]	No significant difference from placebo in reduction of headache days or multiple secondary endpoints.	*Micromedex* Common: cough, URI Serious: rhabdomyolysis. Migraine studies: no difference from placebo PSC: X BF: infant risk cannot be ruled out.		Dose used in study: 80 mg daily. Study did not show efficacy. Would not consider using specifically for migraine prevention.

Table 2. (Continued)

Medication **Type of migraine classification** ***N* completed/*N* randomized** **Study risk of bias classification**	**Efficacy**	**Side effects/adverse events** **Pregnancy safety category (PSC)** **Breastfeeding (BF)**	**Contraindications[a] Caution** **Safety monitoring**	**Dosing** **Populations for consideration**
Alpha adrenergic agonists				
Clonidine MWOA MWA N of 408/507 in meta-analysis [102••] Predominately Class III studies in meta-analysis of 8 RCT [102••] *N* of 408/507 in meta-analysis [102••] Predominately Class III studies in meta-analysis of 8 RCT [102••]	In a meta-analysis clonidine was found to be ineffective in reducing migraine headache frequency [102••]	*Micromedex* Common: hypotension, increased body temperature, constipation, nausea, throat pain, abdominal pain, xerostomia, dizziness, insomnia, sedation, somnolence, otalgia, tinnitus, irritability, nightmares, nasal congestion, URI, fatigue. Serious: AV block PSC: C BF: milk effects are possible.	Avoid in the elderly. Abrupt discontinuation may cause hypertensive crisis. *Monitor*: HR and BP with titration and then periodically	Recommend against using for migraine.
Tizanidine Chronic headache, 77% chronic migraine. 92/134 Class II [40]	Significant reduction versus placebo in headache index, frequency, severity, and duration.	*Micromedex* Common: hypotension, xerostomia, asthemia, dizziness, somnolence. Serious: hepatotoxicity Migraine study: somnolence, dry mouth, dizziness, asthenia PSC: C BF: infant risk cannot be ruled out.	Use of strong CYP1A2 inhibitors Use caution in the elderly, patients with psychiatric disorders, hepatic or rental insufficiency, hypotension, or taking concurrent CNS depressants. *Monitor*: - Renal functioning in elderly patients -Aminotransferase levels in hepatic impairment or suspicion	2 mg daily. Increase by 2 mg every 3 days to max 8 mg TID. Could consider in patients with spasticity or significant myofascial tightness
Guanfacine MWOA		*Micromedex*	Coronary insufficiency, MI, bradycardia, cardiovascular	1 mg daily. Max 2 mg daily.

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
MWA 37/37 (1 site of a 2-site study) Abstract only [39], unable to properly evaluate class.	Significant reduction versus placebo in migraine days/month	Common: hypotension, abdominal pain, constipation, xerostomia, dizziness, headache, insomnia, somnolence, erectile dysfunction, fatigue Serious: bradyarrhythmia, hypotension, syncope, erythroderma, seizure *Migraine Study*: no serious side effects were reported. PSC: B BF: infant risk cannot be ruled out.	disease, heart block, hypotension, syncope Use caution in elderly patients and patients with hepatic or renal impairment *Monitor*: Heart rate and BP with titration and periodically thereafter	Could consider in patients with ADHD
CCBs				
Nicardipine MWOA 30/35 Class II [41]	Significantly more effective than placebo in reducing headache frequency, duration, and intensity	*Micromedex* Common: headache, peripheral edema, hypotension, nausea, vomiting. Serious: MI, acute hepatitis *Migraine study*: headache, dizziness, gastralgia, dyspepsia PSC: C BF: excreted into breast milk. Recommend against use while BF.	Aortic stenosis, heart failure, hypertrophic cardiomyopathy Use caution in the elderly, hepatic, and renal impairment Avoid grapefruit. *Monitor*: BP with titration	Immediate release: 20 mg daily × 7 days then, 20 mg BID
Nimodipine MWA MWOA 3× Class II [47–49] 3× Class III [50, 51, 103] Total *N* = 395/479	3 studies did not show greater efficacy compared with placebo [47, 48, 50] 3 studies did show greater efficacy	*Micromedex* Common: hypotension, headache, diarrhea, nausea. UTDoL: also bradycardia Serious: CHF, GI hemorrhage, DIC, hematoma, hemorrhage. *Migraine studies*:	Hypotension, use of strong CYP3A4 inducers Avoid in hepatic impairment. Avoid grapefruit. Monitor: Heart rate and BP initially and periodically	40 mg TID

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
Meta-analysis of these 6 studies [102••] *N* = 479	compared with placebo [49, 51, 103] Meta-analysis showed nimodipine to be no more effective than placebo.	Vertigo, flushing, itching, weakness, diaphoresis, muscle aches, headache, vasodilatation, dizziness, asthenia, myalgia, depression, abdominal discomfort, weight loss, rash, tachycardia, GI problems. PSC: C BF: excreted into breast milk. Recommend against use while BF.		
Nifedipine MWA MWOA 28/36 Class III [42] MWOA 14/24 Class III [43] Meta-analysis of these 2 studies [102••]	One study shows nifedipine to be effective in significantly reducing headache frequency while the other does not. Meta-analysis showed nimodipine to be no more effective than placebo.	*Micromedex* Common: peripheral edema, flushing, headache, dizziness, nausea palpitations, nervousness hypotension, cough, dyspnea Serious: MI, ventricular arrhythmia, GI obstruction, GI ulcer, aplastic anemia *Migraine studies*: epigastric burning, nervousness, paresthesias, dizziness, peripheral edema, flushing, weight gain, fatigue, mental symptoms. PSC: C BF: excreted into breast milk. Recommend against use while BF.	Cardiogenic shock, use of strong CYP450 inducers, hypotension, aortic stenosis, MI, galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, GI hypomotility. Use caution or avoid in the elderly and in persons with hepatic impairment. Avoid grapefruit. *Monitor*: Liver function periodically.	Immediate release: 30 mg TID-QID. Max dose 120 mg daily Could consider using in patients with Raynaud phenomena
Verapamil MWA MWOA 14/20 Class III [57]	Both studies show mild decrease in headache frequency compared to placebo.	*Micromedex* Common: constipation, headache, dizziness, edema, hypotension, pharyngitis, sinusitis, flu-like symptoms	Hypotension, severe LV dysfunction, Afib/flutter with accessory bypass tract, 2nd|3rd degree AV block, sick	Immediate release: 80 mg TID-QID. Max dose 160 mg TID. Anecdotal evidence for better efficacy of immediate-release versus long acting

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
MWA MWOA 12/23 Class III [58] Meta-analysis with alternative analysis of these 2 studies [102••]	Re-analysis of data indicated that verapamil was not more effective than placebo.	Serious: arrhythmia/AV block, MI, pulmonary edema.= *Migraine studies*: constipation PSC: X BF: infant risk cannot be ruled out.	sinus syndrome, cardiogenic shock Do not use simultaneously with a beta-blocker. Use caution or avoid in the elderly. May reduce neuromuscular transmission. Use caution in neuromuscular disease. May increase blood ethanol levels. *Monitor*: - EKG initially and again once at stable dose—more regularly in renal or hepatic impairment - Liver function periodically	Could consider in migraine with cross-over symptoms with trigeminal autonomic cephalalgias such as periodicity, onset during sleep, unilateral with ipsilateral cranial autonomic features, etc.
Flunarizine[c] MWOA MWA Meta-analysis [102••] of 7 studies [60–64, 104, 105] Total *N* = 332 Meta-analysis [106] of 4 studies [60, 64, 65, 107] Total *N* = 143 Meta-analysis of 7 [60, 62–65, 104, 105] studies [100]	All 3 meta-analyses show flunarizine provided mild improvement in headache frequency over placebo.	Drowsiness, weight gain/increased appetite, depression, anxiety, vomiting, dizziness/vertigo, extrapyramidal symptoms, fatigue, insomnia, motor dysfunction, sedation, sleep disturbance, galactorrhea/prolactinemia, menstrual heartburn, nausea, xerostomia, myalgia, weakness. *Migraine studies:* Somnolence, weight gain No FDA pregnancy category rating, limited human data, no established teratogenicity in	Depression, pre-existing extrapyramidal symptoms, or Parkinson's disease Use caution in hepatic insufficiency. May be porphyrinogenic. *Monitor*: -Depression/suicidal ideation -Extrapyramidal symptoms	5–10 mg daily Max 20 mg TID Consider especially for migraine with vertiginous symptoms

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
		animals, recommend avoiding in pregnancy unless very compelling reason. BF: infant risk cannot be ruled out.		
NMDA receptor antagonists				
Memantine MWOA 52/60 Class I [17•]	Significant improvement on memantine compared to placebo in migraine frequency, severity, and disability.	*Micromedex* Common: constipation, diarrhea, vomiting, confusion, dizziness, headache Serious: cerebrovascular accident, seizure, acute renal failure, pneumonia *Migraine Study* Sedation, drowsiness, vertigo, nausea PSC: B[b] BF: infant risk cannot be ruled out.	Caution advised in severe hepatic impairment, severe renal impairment, elevated urine pH *Monitor*: None	5 mg/day × 7 days, then 10 mg/day Max 20 mg daily Consider especially in elderly patients and patients with memory impairment
Serotonin antagonists				
Cyproheptadine Unclear if both MWA and MWOA were included. 204/259 Class III [69]	Significantly improved migraine frequency, duration, and severity compared to placebo and propranolol.	*Micromedex* Common: increased appetite, weight gain, abdominal discomfort, diarrhea, nausea, vomiting, xerostomia, central nervous system depression, somnolence, thick sputum, bronchial Serious: Hepatitis *Migraine Studies* Weight gain, dry mouth, drowsiness, fatigue, sleep disturbance	Use caution/avoid in the elderly. Angle-closure glaucoma, bladder neck obstruction, elderly—debilitated patients, MAOI concurrent therapy, breastfeeding, infants, pyloroduodenal obstruction, stenosing peptic ulcer, symptomatic prostatic hypertrophy. *Monitor*: Weight	2–4 mg/day increase by 2–4 mg to 4–8 mg/day Max 16 mg/day Could consider in patients with suspected/elevated histamine levels or insomnia

Table 2. (Continued)

Medication Type of migraine classification *N* completed/*N* randomized Study risk of bias classification	Efficacy	Side effects/adverse events Pregnancy safety category (PSC) Breastfeeding (BF)	Contraindications[a] Caution Safety monitoring	Dosing Populations for consideration
		PSC: B BF: infant risk cannot be ruled out.		
Pizotifen[c] MWOA MWA Meta-analysis [102••] of 9 studies [70–73, 108–112] Class II and III Total *N* = 600 Meta-analysis of 4 [71, 72, 74, 113] studies [100] Total *N* = 119	Meta-analysis showed pizotifen was more effective in reducing headache frequency and headache index. [102••] Meta-analysis calculated summary effect size indicates large clinical effect.	*Micromedex* Increased appetite, weight gain, drowsiness *Migraine studies* Weight gain, muscle pain, heavy or restless legs, fluid retention, drowsiness, headache, flushing, reduced libido, worsening of epilepsy, dreaming No FDA PSC rating, limited human data, no teratogenicity in animals, recommend avoiding in pregnancy unless very compelling reason. BF: infant risk cannot be ruled out.	MAOI concurrent therapy, pyloroduodenal obstruction/stenosing pyloric ulcer, lactose or glucose intolerance, glucose malabsorption May be porphyrinogenic. May decrease seizure threshold in epilepsy. *Monitor*: Weight	0.5 mg/day, increase by 0.5 mg to 3–7 days to 0.5 mg TID Max 2 mg TID Could consider in patients with suspected/elevated histamine levels

MWA, migraine with aura; *MWOA*, migraine without aura; *PSC*, pregnancy safety category; *BF*, breastfeeding; *UTDoL*, Up To Date Online

PSC: B, animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women

PSC: C, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

PSC: D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

PSC: X, studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits

[a]Hypersensitivity to the product is a contraindication for every medication

[b]There are no published studies or reports of memantine use during pregnancy in humans

[c]Not available in the USA. Available in Canada

antagonists may exert an anti-migraine effect through the blockade of peripheral afferent activation and reduction of CGRP release. Both of the drugs in this class that have been evaluated for migraine prevention—cyproheptadine and pizotifen—also have anti-histaminergic properties. There are multiple different histamine receptors throughout the nervous system and peripheral immune tissues. Their influence is complex but they are likely to play a role in migraine pathogenesis [99]. It is possible that that the histamine antagonistic action of cyproheptadine and pizotifen plays a role in migraine prevention.

The evidence

The AAN-AHS guideline and supporting systematic review [100] only consider pharmaceuticals available in the USA for which there were randomized control trials with an AAN Class I or II quality of evidence. Specifically, the AAN grading scale is based on perceived risk of bias that could affect the outcome of the study with Class I studies considered to have a low risk of bias, and Class II studies have a moderate risk of bias [101]. The CHS guideline examined "agents commonly used in clinical practice" and used the Grading of Recommendations, Assessment, Development and Evaluation working group (GRADE) methodology [14••]. There are several studies that are not discussed in either of these publications as they were not commonly used for migraine prevention in Canada or the risk of bias in these studies was too high to be considered for inclusion by the AAN-AHS. However, these studies will be mentioned below for the purpose of comprehensiveness. For each of the drug classes, all of the double-blind, randomized controlled trials (DB-RCT) or meta-analyses of such studies are summarized in Table 2 and discussed below.

Alpha-adrenergic agonists—clonidine, tizanidine, guanfacine

There have been 3 alpha-adrenergic agonist medications assessed in DB-RCT for their efficacy in migraine prevention, clonidine (numerous Class II or III, one recent meta-analysis [102••]), tizanidine (1 Class II/fair-quality study) [40], and guanfacine (1 abstract) [39].

With regard to clonidine, AAN-AHS guideline considered 17 studies [22–38] (3 of which included pediatric populations [22, 34, 35]) and concluded that clonidine had limited or no efficacy. In a 2015 meta-analysis of migraine preventive agents, Jackson et al. [102••] report that in each of the 8 double-blind randomized placebo-controlled trials, which met inclusion criteria (all adult investigations), clonidine did not demonstrate superiority in reducing headache frequency. Pooled results also showed lack of efficacy of clonidine at all time points. A high proportion of patients reported side effects when using clonidine; the most common were fatigue and drowsiness.

The study examining tizanidine [40] included patients with chronic daily headache, although 77% of these patients had chronic migraine and the remaining 23% had migrainous (but did not meet criteria for chronic migraine) headache or chronic tension-type headache. Tizanidine was superior to placebo in reducing headache days, intensity, and duration. Side effects included somnolence, dizziness, dry mouth, and asthenia.

The only published report of a DB-RCT examining guanfacine for migraine prevention [39] is an abstract describing the results of patients from 1 of 2 participating sites. In this report, guanfacine was effective in reducing monthly migraine days. No serious side effects were reported, although the abstract suggests that guanfacine is less likely to cause sedation and rebound hypertension than clonidine. It is difficult to assess the quality of this study given that it is only an abstract. Furthermore, the data was never published as a full report making it even more difficult to determine the efficacy of this medication.

ACEIs—lisinopril, enalapril, captopril

There have been 3 ACEIs inhibitors assessed in DB-RCT for their efficacy in migraine prevention, lisinopril (1 Class II/fair-quality study) [19], enalapril (1 Class II/fair-quality study) [16•], and captopril (1 Class III/poor-quality study) [18]. Each was compared against placebo. Each of these studies did show efficacy for migraine prevention. Lisinopril reduced headache hours, headache days, and migraine days. Enalapril reduced headache severity and duration. Captopril reduced a Migraine Index (product of the number of attacks, duration, and severity). Each of these studies reported cough as a significant side effect. Dizziness was also more prevalent when taking lisinopril compared to placebo.

ARBs—candesartan, telmisartan

There have been 2 ARBs assessed in DB-RCT for their efficacy in migraine prevention, candesartan, and telmisartan. Both studies of candesartan (2 Class II/fair-quality studies) [15•, 20] showed it was superior to placebo in reducing headache days or migraine days and in responder rates (percentage of individuals with greater than 50% reduction in headache or migraine days). Candesartan was also evaluated to be non-inferior to propranolol [15•]. The study examining telmisartan (1 Class III/poor-quality study) [21] did not show significant improvement over placebo for the primary endpoint, reduction in the number of migraine days. There were technical issues with the study including a difference in number of migraine days at baseline between the groups and a treatment-by-center interaction. When these were statistically controlled for in a post hoc analysis, telmisartan appeared superior to placebo. In one candesartan study and in the telmisartan study, side effects were reported to be similar to placebo. However, in the more recent candesartan study [15•], candesartan had more side effects than placebo including dizziness, tiredness, and paresthesias.

CCBs—nicardipine, nifedipine, nimodipine, verapamil, flunarizine

There are 5 medications that are classified as CCBs which have been examined in DB-RCTs for their efficacy in migraine prevention in adults—nicardipine, nifedipine, nimodipine, verapamil, and flunarizine. The results in studies examining efficacy for migraine prevention are largely mixed or show only marginal clinical improvement. Side effects were variable but prominent.

CCBs—nicardipine

In one Class II study [41], nicardipine was reported be more effective than placebo at reducing migraine frequency, intensity, and duration. However, when the results from this study were reanalyzed [102••], the confidence interval indicated that nicardipine was not more effective than placebo at reducing headache frequency (intensity and duration were not reanalyzed). Side effects occurring more frequently on nicardipine than placebo included headache and dizziness.

CCBs—nifedipine

The results for the efficacy of nifedipine for migraine prevention have been mixed. Nifedipine has been investigated in 2 Class III placebo-controlled trials [42, 43] and 2 active comparator studies [44, 45] [third comparator study examined by AAN-AHS is open label] [46].

Nifedipine (5 mg three times daily) was more effective than placebo in reducing headache frequency [42] in a Class III study. However, in another Class III study [43], using up to 30 mg three times daily, nifedipine was not superior to placebo in reducing headache frequency. In a meta-analysis of these two studies, nicardipine was not found to be superior to placebo [102••].

Nifedipine has been compared to flunarizine [45], propranolol, and metoprolol [44]. No significant difference was found in the efficacy of nifedipine to flunarizine. Both propranolol and metoprolol were superior to nifedipine, and in this study, nifedipine induced migraine attacks in 71% of patients and only one patient showed improvement.

Interestingly, nifedipine is sometimes used to treat Raynaud disease; in a double-blind, randomized, placebo-control, crossover study examining 8 migraine patients who also had experienced Raynaud phenomenon, results showed a significant improvement in migraine attack severity and frequency in patients taking nifedipine versus placebo [114].

Frequent side effects reported in the placebo-controlled trials were dizziness, edema, and flushing. Other side effects that were reported included epigastric burning, nervousness, paresthesias, mental symptoms, weight gain, and fatigue.

CCBs—nimodipine

The results of nimodipine for migraine prevention are inconsistent. Nimodipine has been compared to placebo in 6 DB-RCT (3 Class II [47–49] and 3 Class III [50, 51, 103] as well as to other medications in 5 DB-RCT [52–56] of which 2 are reported only in abstracts [55, 56]).

Two Class II DB-RCT comparing nimodipine to placebo reported no difference in patients with migraine with aura [47] or migraine without aura [48] when considering migraine frequency or migraine index (migraine days × migraine severity).

However, in another Class II placebo-controlled study [49], nimodipine was superior to placebo in reducing migraine attack frequency and headache index (sum of severity of headaches). There was no difference in headache duration.

Of the 3 Class III double-blind randomized placebo-controlled trials, two reported superiority of nimodipine versus placebo in headache frequency and headache index (headache hours × headache severity) [103] or M Score (M = 2 × (frequency × duration) of disabling headaches + 1 × (frequency × duration) of severe headaches) [51]. Results from another Class III trial indicated that

nimodipine was no more effective than placebo at reducing attack frequency or migraine index [50].

When the results from these studies were pooled, meta-analysis of the results showed that nimodipine was no more effective than placebo in reducing headache frequency [102••].

Nimodipine has also been compared to flunarizine [52], propranolol [53] and pizotifen [54–56] in DB-RCT trials. All of these studies report improvement in migraine measurements over baseline but no significant difference between the two medications.

Side effects reported at a higher frequency with nimodipine over placebo were mild and included vertigo, flushing, itching, muscle aches, abdominal discomfort, and weight loss.

CCBs—verapamil

Verapamil has been compared to placebo in 2 Class III double-blind randomized, placebo-controlled studies [57, 58] and 1 DB-RCT in which it was compared to propranolol and placebo (abstract only) [59]. While verapamil shows some superiority to placebo in each study, the number of participants is small; overall, the benefit of verapamil for migraine prevention is inconclusive.

In one study [57], the weekly headache scores (sum of the peak severity multiplied by the duration of each headache in each week) from 14 patients who completed the study was significantly lower on verapamil compared with placebo, as were the mean number of weekly headaches and headache duration. However, the reductions are of uncertain clinical relevance.

In another study [58], in which 12 patients completed the study, the frequency of migraine headaches per month and the Headache Unit Index (sum of headache severity divided by the total number of days observed) was significantly lower in patients on verapamil compared to placebo.

Results from these two studies were not pooled as they reported their end points at different times; however, a re-analysis of the data showed no difference in reduction compared to placebo of headache days per month in those on verapamil [102••].

In the third study, which was only reported in an abstract [59], results showed that verapamil did not improve headache frequency or headache hours compared to placebo but attack duration was reduced. Although propranolol and verapamil were not statistically difference on any measure, propranolol did show superiority in reducing attack frequency compared to placebo. The number of patients included in this study was not reported and the methodology and statistical analysis was of uncertain quality.

Constipation was the predominant side effect and was frequently reported in patients taking verapamil in these studies. Rash and headache were also reported in those using verapamil.

CCBs—flunarizine

There have been 8 double-blind randomized placebo-controlled trials [60–65, 104, 107, 115] (Class II and III), numerous active comparator studies, and 3 meta-analyses [100, 102••, 106] examining the efficacy of flunarizine for migraine prevention in adults. All placebo-controlled studies demonstrated

superiority for flunarizine for the primary outcome measure. In a meta-analysis pooling the results of 7 of these trials [60–64, 104, 107], flunarizine was superior to placebo in reducing headache frequency and headache index at 8, 12, 16, and 20 weeks but not at 4 weeks [102••]. The greatest reduction achieved in the pooled mean difference of headache days per month was 1.3. However, this report also indicated that flunarizine was comparable in efficacy to all of the medications against which it had been studied in DB-RCTs (propranolol, topiramate, sodium valproate, pizotifen) except for metoprolol, which was evaluated to be superior by meta-analysis of DB-RCTs directly comparing it to flunarizine. Reveiz-Herault et al. [106] also performed a meta-analysis examining the efficacy of flunarizine against placebo and included 4 trials [60, 64, 65, 107]. They concluded that flunarizine was more effective in reducing headache frequency than placebo but found that the monthly difference in attack headache frequency was 0.55 per month. Similarly, Gray et al. [100] performed a meta-analysis on 7 [60, 62–65, 104, 107] of the placebo-controlled trials and determined that flunarizine was more superior than placebo at reducing headache frequency or headache index with an effect size of 0.52 (0.24–0.80). Paterna et al. [115] (not included in these meta-analyses) compared flunarizine to placebo, verapamil, flunarizine, diltiazem, and nimodipine in a crossover design and reported all of these medications were superior to placebo for prevention of migraine, but there was no difference in efficacy between the medications. Somnolence and weight gain are frequently reported side effects of flunarizine.

There are studies which suggest flunarizine has efficacy in reducing the frequency of vertiginous symptoms in vestibular migraine; however, these were randomized comparative trials that were neither placebo-controlled nor double-blinded and therefore, it is difficult to assess the true efficacy of flunarizine for reducing vertiginous symptoms of migraine [116–118].

NMDAR antagonist—memantine

There has been one Class I DB-RCT investigating the efficacy of memantine compared to placebo for migraine prevention [17•]. Memantine was superior to placebo in reducing migraine attack frequency as well as reducing migraine severity and migraine-related disability as measured by the Migraine Disability Assessment Scale (MIDAS). There were no differences between groups in the use of acute pain medication, quality of life scores, or in measures of sleep, depression, and anxiety. Side effects were uncommon and mild and included sedation, drowsiness, mild vertigo, and nausea.

Serotonin antagonists—cyproheptadine, pizotifen

There has been 1 double-blind, randomized, placebo-controlled trial examining the benefit of cyproheptadine for the prevention of migraine in adults [69]; it was compared to both placebo and propranolol in this Class III study. Cyproheptadine was superior to placebo and to propranolol in the reduction of headache frequency, duration, and severity. Side effects of cyproheptadine included weight gain, dry mouth, drowsiness, fatigue, and sleep disturbance.

There have been 13 DB-RCTs comparing pizotifen to placebo [70–74, 108–113, 119, 120], numerous DB-RCTs comparing pizotifen to other medications and 2 meta-analysis examining these studies for migraine prevention in adults

[100, 102••]. The reports of the placebo-controlled trials are Class II or Class III and the majority report superior efficacy of pizotifen over placebo. In one meta-analysis, pizotifen was found to be superior to placebo at all time points in reducing headache frequency and/or headache index [102••]. Additionally, in this same report, calculation of the standardized mean difference in studies comparing pizotifen to metoprolol, flunarizine, divascan, methysergide, nimodipine, naproxen, and prochlorperazine indicates that pizotifen was not significantly different in efficacy for migraine prevention. In another meta-analysis [100], in which 4 studies comparing pizotifen to placebo were included, summary effect size was calculated as 0.91 which the authors report as "indicating a large clinical effect that is highly statistically relevant."

Frequent side effects of pizotifen included drowsiness and weight gain.

Tachyphylaxis

There have been no studies specifically examining the development of tachyphlaxis for any medications when they are used for migraine prophylaxis. Loder and Rizzoli [121] estimate between 1 and 8% of patients will develop tolerance to migraine preventive medications. Multiple explanations for loss of drug effectiveness including both behavioral and physiologic mechanisms are reviewed. Authors Rizzoli and Loder [122] provide an algorithm and recommendations for a clinical approach to addressing development of tolerance to medications for migraine prevention.

Integrating clinical trial results into clinical practice

Decisions regarding which anti-migraine medication to use should be based on patient factors such as medical comorbidities (e.g., depression) and coexistent conditions (e.g., obesity), age, plans to become pregnant or breastfeed, side-effect profiles, and patient preference after education regarding the recommended choices. Headache frequency may also influence the choice of prophylactic medications. Of all of the medications reviewed in this paper, only tizanidine was evaluated in patients with headache on ≥ 15 days per month. Since none of the other medications in these categories have been evaluated in RCTs for chronic migraine, it is not clear if these medications are beneficial for prevention of chronic migraine. However, medications used for the prevention of migraine in patients with < 15 headache days per month are often used in clinical practice in those with chronic migraine as well.

ACEIs and ARBs

ACEIs and ARBs should be considered in patients with hypertension. In patients already receiving anti-hypertensive medications without demonstrated efficacy for migraine prevention, one could consider switching or adding an ACEIs or ARB. There have not been head-to-head comparisons of the individual ACEIs or ARBs for migraine prevention; however, ARBs may be better tolerated than ACEIs. Candesartan has the best evidence for migraine prevention within these classes and it is generally well tolerated. Enalapril and lisinopril appear similar in their efficacy and side-effect profile and the quality of the studies

appears similar. The captopril study used an ACEI equivalent dose that is 3 times higher than the other two studies. Thus, it is difficult to make comparisons or judge its efficacy at a lower dose. If choosing an ACEIs, lisinopril or enalapril are reasonable choices. Common side effects of ACEIs include hypotension, dizziness, and cough and the most common side effects of ARBs are dizziness and fatigue.

ACEIs and ARBs should not be used simultaneously with each other and are contraindicated in patients taking direct-renin inhibitors and in patients with a history of angioedema. Caution should be used in patients with renal artery stenosis, chronic kidney disease, congestive heart failure, or hypotension. ACEIs and ARBs should not be used in patients who are pregnant or planning on becoming pregnant. Breastfeeding is likely safe if using captopril or enalapril but infant risk cannot be ruled out with the other ACEIs and ARBs discussed for migraine prevention.

CCBs

The efficacy of CCBs for migraine prevention is unconvincing. Side effects of CCBs in general are frequent and often a limiting factor, including headache, dizziness, arrhythmia, hypotension, peripheral edema, constipation, and gingival hyperplasia. In general, CCBs are not recommended for migraine prevention. However, flunarizine likely has some benefit and could be considered after other medications have been tried or in patients with prominent vestibular symptoms or hemiplegic migraine. Flunarizine should not be used in patients with major depression, preexisting extrapyramidal syndromes, or Parkinson's disease. Caution should also be exercised with the use of flunarizine in overweight and obese patients. In patients with migraine and troublesome Raynaud's phenomena, nifedipine could be considered. Verapamil is considered effective for the prevention of cluster headache. Verapamil could be considered in patients with migraine and cluster headache, in as well as in patients with migraine that is associated with prominent cranial parasympathetic feature of seasonal rhythmicity. Constipation is a common side effect with verapamil. Contraindications, precautions, and recommendations for monitoring for the individual CCBs are outlined in Table 2. In most cases, CCBs should be avoided in patients who are pregnant or breastfeeding.

Alpha-adrenergic agonists

Tizanidine could be considered in patients with migraine, especially frequent or chronic migraine. It may be particularly beneficial in patients with coexistent myofascial pain, cramping, or spasm. Somnolence, dry mouth, and dizziness are common side effects. Tizanidine can also cause hallucinations. Caution should be used in patients with psychiatric disorders, hepatic or renal insufficiency, hypotension, or in combination with other CNS depressants. Tizanidine should be avoided during pregnancy, and the risk to the breastfed infants is uncertain.

Clonidine is not recommended for migraine prevention.

The evidence for use of guanfacine in migraine is inconclusive. In patients with ADHD and migraine, guanfacine could be tried. Common side effects include fatigue, somnolence, insomnia, headache, erectile dysfunction, dry

mouth, hypotension, and dizziness. It should be avoided in patients with hepatic or renal impairment, cardiovascular conditions including bradycardia, AV block, cardiac conduction disturbances, cerebrovascular disease, coronary artery disease, recent myocardial infarction, hypotension, and orthostatic hypotension. It should not be discontinued abruptly as rebound hypertensive crisis is possible. Guanfacine has been rated by the FDA as pregnancy safety category B: animal reproduction studies have *failed* to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Guanfacine should be avoided in mothers who are breastfeeding as infant risk is uncertain.

NMDAR antagonists

Memantine may be used for migraine prevention and is generally well tolerated. It may be especially useful in the elderly or in patients with cognitive/memory impairment. It should be avoided in patients with severe hepatic or renal impairment or in patients with alkaluria. Side effects include gastrointestinal upset (vomiting, diarrhea, constipation), dizziness, and sedation. While memantine is rated by the FDA as pregnancy safety category B, indicating no proven risk in humans, this drug is FDA approved for use in Alzheimer's disease which does not usually affect women of childbearing age, and while used off-label in some other conditions, there have been no published safety reports with its use in humans during pregnancy. Risk to the infant cannot be ruled out if used during breastfeeding.

Serotonin antagonists

While there is good evidence for the efficacy of pizotifen for migraine prevention in adults and considerably less but still positive results for cyproheptadine, these medications are infrequently used for migraine prevention in adults. This is predominantly due to frequent side effects of weight gain and somnolence. However, because of their anti-histaminergic action, they could still be considered in those with coexistent disorders associated with elevated histamine (e.g., allergic diatheses, mast cell activation syndrome). Use caution in prescribing to the elderly, overweight, or obese patients, in patients with conditions that could be worsened by weight gain (e.g., diabetes, hypertension) or patients in whom somnolence could be dangerous (e.g., truck and taxi drivers, heavy machinery operators, air traffic controllers). Cyproheptadine is FDA rated as pregnancy safety category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Pizotifen is not rated by the FDA as it is not available in the USA. There is limited human data and no teratogenicity has been shown in animals. In breastfeeding mothers using these serotonin antagonists, infant risk is unknown.

Summary

Preventive anti-migraine treatments should be considered in patients who have more than 3 days of migraine per month and in individuals with substantial migraine-related impairment. In addition to behavioral and lifestyle modifications, pharmaceutical therapies are effective for migraine prevention. Choice of

preventive medication should take into account the patient history, comorbid and coexistent conditions, personal preference, and pregnancy plans. ACEIs, ARBs, CCBs, NMDAR antagonists, serotonin antagonists, and alpha-adrenergic agonists may be considered for migraine prevention in selected patients. Given the somewhat poor level of evidence for the efficacy of many of the medications in these classes, one might think that they should not be used as first-line treatment against migraine. This is probably true in an otherwise healthy individual, without comorbidities and preconceived notions. However, in a patient with migraine, hypertension and diabetes, an ACEI or an ARB may be an ideal first line treatment to help minimize the number of needed medications. It is also not uncommon to encounter patients who have strong aversion to the concept of taking an antidepressant medication or an antiepileptic medication. There are many other instances where one may find it beneficial to consider "alternative" medications, and thus being familiar with the range of preventive migraine treatments can be quite helpful.

Within these classes of medications, candesartan, memantine, and pizotifen have a moderate level of evidence of efficacy; candesartan and memantine are generally well tolerated. Clonidine is not recommended for migraine prevention and CCBs should only be used in certain clinical situations (see text and Table 2).

Compliance with Ethical Standards

Conflict of Interest

David W. Dodick reports the following conflicts from within the past 48 months. Personal fees: Amgen, Autonomic technologies, Axsome, Allergan, Alder, Biohaven, Charleston Laboratories, Dr. Reddy's Laboratories/Promius, Electrocore LLC, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Sun Pharma (India), Theranica, Teva, Vedanta, WL Gore, Zosano, ZP Opco, Foresite Capital, Oppenheimer, Arteaus, Pfizer, Colucid, Merck, NuPathe, Ethicon J&J, Zogenix, Labrys, Boston Scientific, Medtronic, St. Jude, Bristol-Myers Squibb, Lundbeck, Impax, MAP, Tonix, Alcobra, Insys, Acorda, Biocentric, Magellan, Xenon, CC Ford West Group, IntraMed, SAGE Publishing, Sun Pharma, American Academy of Neurology, Decision Resources, Synergy, Peer View Institute for Medical Education, MeetingLogiX, Wiley Blackwell. CME fees or Royalty payments: Healthlogix, Medicom, Medlogix, Mednet, Miller Medical, PeerView, WebMD/Medscape, Chameleon, Academy for Continued Healthcare Learning, Universal meeting management, Haymarket, Global Scientific Communications, UpToDate, Oxford University Press, Cambridge University Press, Wolters Kluwer Equity (stock options): Aural analytics, Healint, Theranica, Second Opinon/Mobile Health, Epien, GBS/Nocira, Matterhorn/Ontologics, King-Devick Technologies. Board of Directors: Aural analytics, Epien, Matterhorn/Ontologics, King-Devick Technologies. Patent: 17189376.1-1466:v Title: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Professional society fees or reimbursement for travel: American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, International Headache Society, Canadian Headache Society. Other: use agreement through employer Myndshft. Expense reimbursement from West Virginia University Foundation, Oregon Health Science Center, Albert Einstein University, University of Toronto, Starr Clinical, University of British Columbia, University of Southern California, and University of California, Los Angeles. Consulting use agreement through employer: Neuro-Assessment Systems.

Jill C. Rau reports personal fees from speaking at an Amgen sponsored educational event on a general topic outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013;53(3):427–36. https://doi.org/10.1111/head.12074.
2. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (London, England). 2017;390(10100):1211–59. https://doi.org/10.1016/s0140-6736(17)32154-2.
3. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Arch Intern Med. 1999;159(8):813–8.
4. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343–9. https://doi.org/10.1212/01.wnl.0000252808.97649.21.
5. Andrasik F. What does the evidence show? Efficacy of behavioural treatments for recurrent headaches in adults. Neurol Sci. 2007;28(Suppl 2):S70–7. https://doi.org/10.1007/s10072-007-0754-8.
6. Probyn K, Bowers H, Mistry D, Caldwell F, Underwood M, Patel S, et al. Non-pharmacological self-management for people living with migraine or tension-type headache: a systematic review including analysis of intervention components. BMJ Open. 2017;7(8):e016670. https://doi.org/10.1136/bmjopen-2017-016670.
7.• Rosenberg L, Butler N, Seng EK. Health behaviors in episodic migraine: why behavior change matters. Curr Pain Headache Rep. 2018;22(10):65. https://doi.org/10.1007/s11916-018-0721-5.

These authors highlight lifestyle and behavioral changes that are beneficial for reducing migraine burden.

8. Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. Headache. 2007;47(8):1178–83. https://doi.org/10.1111/j.1526-4610.2007.00780.x.
9. Kristoffersen ES, Straand J, Russell MB, Lundqvist C. Lasting improvement of medication-overuse headache after brief intervention - a long-term follow-up in primary care. Eur J Neurol. 2017;24(7):883–91. https://doi.org/10.1111/ene.13318.
10.• Buse DC, Andrasik F. Behavioral medicine for migraine. Neurol Clin. 2009;27(2):445–65. https://doi.org/10.1016/j.ncl.2009.01.003.

This paper reviews the evidence for behavioral therapies for migraine prevention.

11.• Grimsrud KW, Halker Singh RB. Emerging treatments in episodic migraine. Curr Pain Headache Rep. 2018;22(9):61. https://doi.org/10.1007/s11916-018-0716-2

This paper describes available and upcoming neuromodulatory treatments for migraine.

12.•• Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. 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(17):1337–45. https://doi.org/10.1212/WNL.0b013e3182535d20.

These are the most up-to-date guidelines in the United States for the prevention of episodic migraine in adults.

13. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the guideline development subcommittee of the American Academy of neurology. Neurology. 2016;86(19):1818–26. https://doi.org/10.1212/WNL.0000000000002560.
14.•• Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012;39(2 Suppl 2):S1–59.

These are the most up-to-date guidelines in Canada for the prevention of episodic migraine in adults.

15.• Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014;34(7):523–32. https://doi.org/10.1177/0333102413515348.
This study reports efficacy of the ARB, candesartan, for migraine prophylaxis. It was published after both of the recent North American guidelines for migraine prevention in adults and lend additional evidence for the safety, tolerability and efficacy of candesartan for migraine prevention.
16.• Sonbolestan SA, Heshmat K, Javanmard SH, Saadatnia M. Efficacy of enalapril in migraine prophylaxis: a randomized, double-blind, placebo-controlled trial. Int J Prev Med. 2013;4(1):72–7.
This study reports efficacy of the NMDAR-antagonist, memantine, for migraine prophylaxis. It was published after both of the recent North American guidelines for migraine prevention in adults. It introduces good evidence for the use of a different class of medication for migraine prevention.
17.• Noruzzadeh R, Modabbernia A, Aghamollaii V, Ghaffarpour M, Harirchian MH, Salahi S, et al. Memantine for prophylactic treatment of migraine without aura: a randomized double-blind placebo-controlled study. Headache. 2016;56(1):95–103. https://doi.org/10.1111/head.12732.
This study reports efficacy of the NMDAR-antagonist, memantine, for migraine prophylaxis. It was published after both of the recent North American guidelines for migraine prevention in adults. It introduces good evidence for the use of a different class of medication for migraine prevention.
18. Paterna S, di Pasquale P, Martino S, Arrostuto A, Ingurgio NC, Parrinello G, et al. Captopril versus placebo in the prevention of hemicrania without aura. A randomized double-blind study. Clin Ter. 1992;141(12):475–81.
19. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ (Clin Res). 2001;322(7277):19–22.
20. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA. 2003;289(1):65–9.
21. Diener HC, Gendolla A, Feuersenger A, Evers S, Straube A, Schumacher H, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia. 2009;29(9):921–7. https://doi.org/10.1111/j.1468-2982.2008.01825.x.
22. Adam EI, Gore SM, Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. J R Coll Gen Pract. 1978;28(195):587–90.
23. Anthony M, Lance JW, Somerville B. A comparative trial of prindolol, clonidine and carbamazepine in the interval therapy of migraine. Med J Aust. 1972;1(26):1343–6.
24. Boisen E, Deth S, Hubbe P, Jansen J, Klee A, Leunbach G. Clonidine in the prophylaxis of migraine. Acta Neurol Scand. 1978;58(5):288–95.
25. Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. A randomized crossover trial. J Fam Pract. 1989;29(2):153–6. discussion 7-8.
26. Das SM, Ahuja GK, Narainaswamy AS. Clonidine in prophylaxis of migraine. Acta Neurol Scand. 1979;60(4):214–7.
27. Kallanranta T, Hakkarainen H, Hokkanen E, Tuovinen T. Clonidine in migraine prophylaxis. Headache. 1977;17(4):169–72.
28. Kass B, Nestvold K. Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine. A comparative trial. Acta Neurol Scand. 1980;61(6):351–6.
29. Louis P, Schoenen J, Hedman C. Metoprolol v. clonidine in the prophylactic treatment of migraine. Cephalalgia. 1985;5(3):159–65. https://doi.org/10.1046/j.1468-2982.1985.0503159.x.
30. Lynggaard F, Ostergaard F. [Clonidine in prevention of migraine. Report of a double-blind study of 38 patients referred for neurological assessment]. Ugeskr Laeger. 1975;137(3):149–51.
31. Mondrup K, Moller CE. Prophylactic treatment of migraine with clonidine. A controlled clinical trial. Acta Neurol Scand. 1977;56(5):405–12.
32. Ryan RE Sr, Diamond S, Ryan RE Jr. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache. 1975;15(3):202–10.
33. Shafar J, Tallett ER, Knowlson PA. Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet (London, England). 1972;1(7747):403–7.
34. Sillanpaa M. Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children. Headache. 1977;17(1):28–31.
35. Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine: a pilot and double-blind study. Dev Med Child Neurol. 1982;24(6):837–41.
36. Sjaastad O, Stensrud P. 2-(2.6-dichlorophenylamino)-2-imidazoline hydrochloride (ST 155 or Catapresan) as a prophylactic remedy against migraine. Acta Neurol Scand. 1971;47(1):120–2.
37. Stensrud P, Sjaastad O. Clonidine (Catapresan)-double-blind study after long-term treatment with the drug in migraine. Acta Neurol Scand. 1976;53(3):233–6.
38. Wilkinson M. Preliminary report on the use of clonidine (Boehringer Ingelheim) in the treatment of migraine. Res Clin Stud Headache. 1970;3:315–20.
39. Elkind AH, Webster C, Herbertson RK. Efficacy of guanfacine in a double blind parallel study for migraine prophylaxis. Cephalalgia. 1989;9(Suppl. 10).
40. Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache. 2002;42(6):470–82.
41. Leandri M, Rigardo S, Schizzi R, Parodi CI. Migraine treatment with nicardipine. Cephalalgia.

1990;10(3):111–6. https://doi.org/10.1046/j.1468-2982.1990.1003111.x.
42. Shukla R, Garg RK, Nag D, Ahuja RC. Nifedipine in migraine and tension headache: a randomised double blind crossover study. J Assoc Physicians India. 1995;43(11):770–2.
43. McArthur JC, Marek K, Pestronk A, McArthur J, Peroutka SJ. Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. Neurology. 1989;39(2 Pt 1):284–6.
44. Gerber WD, Diener HC, Scholz E, Niederberger U. Responders and non-responders to metoprolol, propranolol and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. Cephalalgia. 1991;11(1):37–45. https://doi.org/10.1046/j.1468-2982.1991.1101037.x.
45. Lamsudin R, Sadjimin T. Comparison of the efficacy between flunarizine and nifedipine in the prophylaxis of migraine. Headache. 1993;33(6):335–8.
46. Albers GW, Simon LT, Hamik A, Peroutka SJ. Nifedipine versus propranolol for the initial prophylaxis of migraine. Headache. 1989;29(4):215–8.
47. European multicenter trial of nimodipine in the prophylaxis of classic migraine (migraine with aura). Migraine-Nimodipine European Study Group (MINES). Headache. 1989;29(10):639–42.
48. European multicenter trial of nimodipine in the prophylaxis of common migraine (migraine without aura). Migraine-Nimodipine European Study Group (MINES). Headache. 1989;29(10):633–8.
49. Havanka-Kanniainen H, Hokkanen E, Myllyla VV. Efficacy of nimodipine in the prophylaxis of migraine. Cephalalgia. 1985;5(1):39–43. https://doi.org/10.1046/j.1468-2982.1985.0501039.x.
50. Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, et al. Nimodipine in migraine prophylaxis. Cephalalgia. 1988;8(4):269–72. https://doi.org/10.1046/j.1468-2982.1988.0804269.x.
51. Gelmers HJ. Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache. 1983;23(3):106–9.
52. Bussone G, Baldini S, D'Andrea G, Cananzi A, Frediani F, Caresia L, et al. Nimodipine versus flunarizine in common migraine: a controlled pilot trial. Headache. 1987;27(2):76–9.
53. Formisano R, Falaschi P, Cerbo R, Proietti A, Catarci T, D'Urso R, et al. Nimodipine in migraine: clinical efficacy and endocrinological effects. Eur J Clin Pharmacol. 1991;41(1):69–71. https://doi.org/10.1007/bf00280110.
54. Havanka-Kanniainen H, Hokkanen E, Myllyla VV. Efficacy of nimodipine in comparison with pizotifen in the prophylaxis of migraine. Cephalalgia. 1987;7(1):7–13. https://doi.org/10.1046/j.1468-2982.1987.0701007.x.
55. Micieli G, Tucco M, Agostinis C, Mancuso A, Papalia F, Sinforiani E. Nimodipine vs. pizotifen in common migraine: results of a double-clind cross-over trial. Cephalalgia. 1985;5(Suppl 3):532–3.
56. Gawel MJ. A double-blind, cross over study of nimopidipine versus pizotyline in a common and classical migraine. Cephalalgia. 1987;7(Suppl 6):453–4.
57. Markley HG, Cheronis JC, Piepho RW. Verapamil in prophylactic therapy of migraine. Neurology. 1984;34(7):973–6.
58. Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. JAMA. 1983;250(18):2500–2.
59. Solomon GD. Verapamil and propranolol in migraine prophylaxis: a double blind crossover study. Headache. 1986;26.
60. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. Headache. 1981;21(6):235–9.
61. Frenken CW, Nuijten ST. Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. Clin Neurol Neurosurg. 1984;86(1):17–20.
62. Mentenopoulos G, Manafi T, Logothetis J, Bostantzopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia. 1985;5(Suppl 2):135–40. https://doi.org/10.1177/03331024850050s225.
63. Sorensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia. 1986;6(1):7–14. https://doi.org/10.1046/j.1468-2982.1986.0601007.x.
64. Thomas M, Behari M, Ahuja GK. Flunarizine in migraine prophylaxis: an Indian trial. Headache. 1991;31(9):613–5.
65. al Deeb SM, Biary N, Bahou Y, al Jaberi M, Khoja W. Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population). Headache. 1992;32(9):461–2.
66. Cerbo R, Casacchia M, Formisano R, Feliciani M, Cusimano G, Buzzi MG, et al. Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis. Cephalalgia. 1986;6(1):15–8. https://doi.org/10.1046/j.1468-2982.1986.0601015.x.
67. Louis P, Spierings EL. Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: a double-blind study. Cephalalgia. 1982;2(4):197–203. https://doi.org/10.1046/j.1468-2982.1982.0204197.x.
68. Rascol A, Montastruc JL, Rascol O. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. Headache. 1986;26(2):83–5.
69. Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurol India. 2000;48(3):223–6.
70. Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache. 1990;30(11):710–5.

71. Lawrence ER, Hossain M, Littlestone W. Sanomigran for migraine prophylaxis, controlled multicenter trial in general practice. Headache. 1977;17(3):109–12.
72. Osterman PO. A comparison between placebo, pizotifen and 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2.3.5.6-tetrahydroindol (Divascan) in migraine prophylaxis. Acta Neurol Scand. 1977;56(1):17–28.
73. Carroll JD, Maclay WP. Pizotifen (BC 105) in migraine prophylaxis. Curr Med Res Opin. 1975;3(2):68–71. https://doi.org/10.1185/03007997509113649.
74. Sjaastad O, Stensrud P. Appraisal of BC-105 in migraine prophylaxis. Acta Neurol Scand. 1969;45(5):594–600.
75.• Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17(2):174–82. https://doi.org/10.1016/S1474-4422(17)30435-0.

This is an exceptional and recent review of the current understanding of migraine pathophysiology.

76.• Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: Evidence review and clinical implications. Cephalalgia. 2019:333102418821662. https://doi.org/10.1177/0333102418821662.

This paper reviews the newest class of migraine preventive medications which were designed specifically for migraine, are targeted against CGRP receptors or ligand and were released in the past year.

77. Moldovan Loomis C, Dutzar B, Ojala EW, Hendrix L, Karasek C, Scalley-Kim M, et al. Pharmacologic characterization of ALD1910, a potent humanized monoclonal antibody against the pituitary adenylate cyclase activating peptide. J Pharmacol Exp Ther. 2019. https://doi.org/10.1124/jpet.118.253443.
78. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol. 2006;59(4):652–61. https://doi.org/10.1002/ana.20778.
79. Philipp M, Brede M, Hein L. Physiological significance of alpha(2)-adrenergic receptor subtype diversity: one receptor is not enough. Am J Physiol Regul Integr Comp Physiol. 2002;283(2):R287–95. https://doi.org/10.1152/ajpregu.00123.2002.
80. Ginsburg J, O'Reilly B, Swinhoe J. Effect of oral clonidine on human cardiovascular responsiveness: a possible explanation of the therapeutic action of the drug in menopausal flushing and migraine. Br J Obstet Gynaecol. 1985;92(11):1169–75.
81. Fairbanks CA, Stone LS, Kitto KF, Nguyen HO, Posthumus IJ, Wilcox GL. Alpha(2C)-adrenergic receptors mediate spinal analgesia and adrenergic-opioid synergy. J Pharmacol Exp Ther. 2002;300(1):282–90.
82. Lavand'homme PM, Ma W, De Kock M, Eisenach JC. Perineural alpha(2A)-adrenoceptor activation inhibits spinal cord neuroplasticity and tactile allodynia after nerve injury. Anesthesiology. 2002;97(4):972–80.
83. Ripa P, Ornello R, Pistoia F, Carolei A, Sacco S. The renin-angiotensin system: a possible contributor to migraine pathogenesis and prophylaxis. Expert Rev Neurother. 2014;14(9):1043–55. https://doi.org/10.1586/14737175.2014.946408.
84. Pietrobon D. Calcium channels and migraine. Biochim Biophys Acta. 2013;1828(7):1655–65. https://doi.org/10.1016/j.bbamem.2012.11.012.
85. Monzani D, Genovese E, Pini LA, Di Berardino F, Alicandri Ciufelli M, Galeazzi GM, et al. Nimodipine in otolaryngology: from past evidence to clinical perspectives. Acta Otorhinolaryngol Ital. 2015;35(3):135–45.
86. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell. 1996;87(3):543–52.
87. Pelzer N, Stam AH, Haan J, Ferrari MD, Terwindt GM. Familial and sporadic hemiplegic migraine: diagnosis and treatment. Curr Treat Options Neurol. 2013;15(1):13–27. https://doi.org/10.1007/s11940-012-0208-3.
88. Ambrosio C, Stefanini E. Interaction of flunarizine with dopamine D2 and D1 receptors. Eur J Pharmacol. 1991;197(2–3):221–3.
89. Marmura MJ. Use of dopamine antagonists in treatment of migraine. Curr Treat Options Neurol. 2012;14(1):27–35. https://doi.org/10.1007/s11940-011-0150-9.
90. DaSilva AF, Nascimento TD, Jassar H, Heffernan J, Toback RL, Lucas S, et al. Dopamine D2/D3 imbalance during migraine attack and allodynia in vivo. Neurology. 2017;88(17):1634–41. https://doi.org/10.1212/wnl.0000000000003861.
91. Wober C, Brucke T, Wober-Bingol C, Asenbaum S, Wessely P, Podreka I. Dopamine D2 receptor blockade and antimigraine action of flunarizine. Cephalalgia. 1994;14(3):235–40. https://doi.org/10.1046/j.1468-2982.1994.014003235.x.
92. Rothrock JF, Mar KR, Yaksh TL, Golbeck A, Moore AC. Cerebrospinal fluid analyses in migraine patients and controls. Cephalalgia. 1995;15(6):489–93. https://doi.org/10.1046/j.1468-2982.1995.1506489.x.
93. Martinez F, Castillo J, Rodriguez JR, Leira R, Noya M. Neuroexcitatory amino acid levels in plasma and cerebrospinal fluid during migraine attacks. Cephalalgia. 1993;13(2):89–93. https://doi.org/10.1046/j.1468-2982.1993.1302089.x.
94. Charles A, Brennan K. Cortical spreading depression-new insights and persistent questions. Cephalalgia. 2009;29(10):1115–24. https://doi.org/10.1111/j.1468-2982.2009.01983.x.
95. Oshinsky ML, Luo J. Neurochemistry of trigeminal activation in an animal model of migraine. Headache. 2006;46(Suppl 1):S39–44.
96. Hoffmann J, Charles A. Glutamate and its receptors as therapeutic targets for migraine. Neurotherapeutics. 2018;15(2):361–70. https://doi.org/10.1007/s13311-018-0616-5.

97. Ramadan NM. Glutamate and migraine: from Ikeda to the 21st century. Cephalalgia. 2014;34(2):86–9. https://doi.org/10.1177/0333102413499646.
98. Kilinc E, Guerrero-Toro C, Zakharov A, Vitale C, Gubert-Olive M, Koroleva K, et al. Serotonergic mechanisms of trigeminal meningeal nociception: implications for migraine pain. Neuropharmacology. 2017;116:160–73. https://doi.org/10.1016/j.neuropharm.2016.12.024.
99. Yuan H, Silberstein SD. Histamine and migraine. Headache. 2018;58(1):184–93. https://doi.org/10.1111/head.13164.
100. Gray RN, Goslin RE, McCrory DC, Eberlein K, Tulsky J, Hasselblad V. AHRQ Technical Reviews. Drug treatments for the prevention of migraine headache. Rockville (MD): Agency for Health Care Policy and Research (US); 1999.
101. Neurology AAo. Clinical Practice Guideline Process Manual. St. Paul: The American Academy of Neurology; 2011.
102.•• Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. PloS One. 2015;10(7):e0130733. https://doi.org/10.1371/journal.pone.0130733.

This is a comprehensive systematic review of oral medications used for migraine propylaxis.

103. Stewart DJ, Gelston A, Hakim A. Effect of prophylactic administration of nimodipine in patients with migraine. Headache. 1988;28(4):260–2.
104. Diamond S, Freitag FG. A double-blind trial of flunarizine in migraine prophylaxis. Headac Q. 1992;4:169–72.
105. Pini LA, Ferrari A, Guidetti G, Galetti G, Barbieri L, Sternieri E. Effectiveness of flunarizine in altering electronystagmographic patterns in migraine patients: a preliminary report. Int J Clin Pharmacol Res. 1986;6(1):27–32.
106. Reveiz-Herault L, Cardona AF, Ospina EG, Carrillo P. [Effectiveness of flunarizine in the prophylaxis of migraine: a meta-analytical review of the literature]. Rev Neurol. 2003;36(10):907–12.
107. Pini LA, Ferrari A, Guidetti G, Galetti G, Sternieri E. Influence of flunarizine on the altered electronystagmographic (ENG) recordings in migraine. Cephalalgia. 1985;5(Suppl 2):173–5. https://doi.org/10.1177/03331024850050s233.
108. Arthur GP, Hornabrook RW. The treatment of migraine with BC 105 (pizotifen): a double blind trial. N Z Med J. 1971;73(464):5–9.
109. Cleland PG, Barnes D, Elrington GM, Loizou LA, Rawes GD. Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. Eur Neurol. 1997;38(1):31–8. https://doi.org/10.1159/000112899.
110. Hughes RC, Foster JB. BC 105 in the prophylaxis of migraine. Curr Ther Res Clin Exp. 1971;13(1):63–8.
111. Kangasniemi P. Placebo, 1-isopropylnoradrenochrome-5-monosemicarbazono and pizotifen in migraine prophylaxis. Headache. 1979;19(4):219–22.
112. Ryan RE. Double-blind crossover comparison of bc-105, methysergide and placebo in the prophylaxis of migraine headache. Headache. 1968;8(3):118–26.
113. Krakowski AJ, Engisch R. A new agent for chemotherapy of migraine headaches: a controlled study. Psychosomatics. 1973;14(5):302–8. https://doi.org/10.1016/S0033-3182(73)71324-4.
114. Kahan A, Weber S, Amor B, Guerin F, Degeorges M. Nifedipine in the treatment of migraine in patients with Raynaud's phenomenon. N Engl J Med. 1983;308(18):1102–3.
115. Paterna S, Martino SG, Campisi D, Cascio Ingurgio N, Marsala BA. [Evaluation of the effects of verapamil, flunarizine, diltiazem, nimodipine and placebo in the prevention of hemicrania. A double-blind randomized cross-over study]. Clin Ter. 1990;134(2):119–25.
116. Yuan Q, Liu DL, Yu LS, Zhang QF. [Flunarizine in the prophylaxis of vestibular migraine:a randomized controlled trial]. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2016;30(10):805–10. https://doi.org/10.13201/j.issn.1001-1781.2016.10.012.
117. Liu F, Ma T, Che X, Wang Q, Yu S. The efficacy of venlafaxine, flunarizine, and valproic acid in the prophylaxis of vestibular migraine. Front Neurol. 2017;8:524. https://doi.org/10.3389/fneur.2017.00524.
118. Lepcha A, Amalanathan S, Augustine AM, Tyagi AK, Balraj A. Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. Eur Arch Otorhinolaryngol. 2014;271(11):2931–6. https://doi.org/10.1007/s00405-013-2786-4.
119. Lance JW, Anthony M. Clinical trial of a new serotonin antagonist, BC105, in the prevention of migraine. Med J Aust. 1968;1(2):54–5.
120. Ryan RE. BC-105 a new preparation for the interval treatment of migraine–a double blind evaluation compared with a placebo. Headache. 1971;11(1):6–18.
121. Rizzoli P, Loder EW. Tolerance to the beneficial effects of prophylactic migraine drugs: a systematic review of causes and mechanisms. Headache. 2011;51(8):1323–35. https://doi.org/10.1111/j.1526-4610.2011.01985.x.
122. Loder EW, Rizzoli P. Tolerance and loss of beneficial effect during migraine prophylaxis: clinical considerations. Headache. 2011;51(8):1336–45. https://doi.org/10.1111/j.1526-4610.2011.01986.x.