

## Pharmacologic treatment for migraines-where are we now?

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### **Abstract**

**Background:** *The most common type of headache that propels patients to seek care from their clinician is a migraine headache. Migraine headaches vary from person to person, but they typically last from four hours to 72 hours. A migraine may occur with symptoms such as nausea, vomiting, or sensitivity to light. Patients may get migraines several times per month while other patients may get them much more frequently. Migraine headaches have no known cure, but in most cases they can be managed effectively with a variety of medications and/or alternative modalities for prevention, pain relief and abortive therapy.*

**Objective:** *Recently the American Academy of Neurology and the American Headache Society updated pharmacologic treatment guidelines for episodic migraine prevention in adults. These guidelines were presented at the April 2012 meeting of the American Academy of Neurology. This article will review the recommendations from the American Academy of Neurology and the American Headache Society that were presented at their April 2012 meeting.*

**Methods:** *Retrospective published studies and current empirical knowledge from June 1999 to May 2009 were reviewed by authors from the American Academy of Neurology and the American Headache Society to establish and classify evidence related to the efficacy of various medications available in the United States for migraine prevention.*

**Results:** *After review of 284 abstracts, the author panel from the American Academy of Neurology and the American Headache Society found 29 Class I or Class II articles to review. This appraisal yielded seven pharmacologic agents that should be offered to patients for migraine prevention, migraine frequency and/or migraine severity: divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, timolol, and frovatriptan for prevention of menstrual migraine (Level A).*

**Keywords—***Migraine, American Academy of Neurology, American Headache Society, evidence-based recommendations, pharmacologic treatment of migraines*

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### I. INTRODUCTION

Worldwide, according to the World Health Organization (WHO) <sup>[1]</sup>, migraine alone is 19th among all causes of years lived with disability (YLDs). Migraine mostly affects patients between 35 and 45 years of age however, migraines can afflict much younger patients, including children <sup>[1]</sup>. Migraine is a chronic disorder characterized by moderate to severe headaches and photophobia, phonophobia, nausea and/or vomiting; some believe migraine is a neurological disorder, however there is no evidence to confirm this theory <sup>[2]</sup>. At the present time the cause of migraines is unknown; however the most supported theory is that it is related to hyperexcitability of the cerebral cortex and/or abnormal control of pain neurons in the trigeminal nucleus of the brainstem. <sup>[3]</sup>

The patient with a migraine typically presents with recurrent severe headache associated with autonomic symptoms. <sup>[4]</sup> For each patient, the severity of the pain, duration of the headache, and frequency of the attacks is variable. Migraineurs can experience four possible phases in a migraine attack with aura: (1) the prodrom (which occurs hours or days before the headache), (2) the aura (which immediately precedes the headache), (3) the pain phase (also known as the headache phase), and (4) the prodrome. <sup>[5]</sup> Alternatively, the diagnosis of migraine without aura, according to the International Headache Society (IHS) can be made according to the mnemonic "54321 criteria": (a) five or more attacks – for migraine with aura, two attacks are sufficient for diagnosis, (b) four hours to three days in duration, (c) two or more of the following, unilateral, pulsating, moderate or severe pain intensity, aggravation by/or causing avoidance of routine physical activity, and (d) one or more of the following, nausea and/or vomiting, sensitivity to both light and sound. <sup>[5]</sup>

Preventive treatment of migraine is an important part of migraine management. The goal of preventative therapy is to reduce the frequency, pain, and/or duration of migraine and increase the effectiveness of abortive therapy. <sup>[6]</sup> Preventative therapy can include medication, surgery, alternative therapies, acupuncture, acupressure, herbs, medical devices and/or the utilization of a migraine diary. This paper will review the

pharmacologic treatment of episodic migraines as developed in 2012 by American Academy of Neurology (AAN) and the American Headache Society (AHS).

## II. ANALYTIC PROCESS

Guidelines were established for migraine prevention in 2000 by the AAN. Evidence identified in formulating the previous guidelines in 2000 was supplemented with evidence from a new search that extended through the middle of 2009, and classification criteria included only studies with completion rates above 80%. The AHS/AAN guidelines of 2012 are the result of a systematic search, expert review, and synthesis of relevant evidence for preventive treatments of episodic migraine by authors from the AHS/ AAN.

An author panel of headache and methodologic experts from the AAN and AHS was assembled to review the evidence and computerized searches of the MEDLINE, PsycINFO, and CINAHL databases identified new studies (published in English).<sup>[7]</sup> The MeSH term “headache” (exploded) and a published search strategy for identifying randomized controlled trials (RCTs) published between June 1999 and May 2007 was utilized by the author panel.<sup>[7]</sup> Studies of pharmacologic agents available in the United States were included in the analysis if they randomized adult patients with migraine to the agent under study or a comparator drug (including placebo) and utilized masked outcome assessment.<sup>[7]</sup>

Prescription drugs were then categorized into the following categories; Level A: Medications with Established Efficacy ( $\geq$  Two Class I Trials), Level B: medications are probably effective (1 class I/or two Class II studies), Level C: medications are possibly effective (1 class II study), Level U: Inadequate or conflicting data to support or refute medication use, and Other: medications that are established as possibly or probably ineffective (see table 1).<sup>[7]</sup>

The original and supplemental search of 284 articles yielded a total of 29 medications that were potentially effective for migraine prevention and were classified as Class I or Class II. Studies were excluded if they: assessed the efficacy of therapeutic agents for headache other than episodic migraine in adults, assessed acute migraine treatment, migraine aura treatment/prevention, or nonpharmacologic treatments (e.g., behavioral approaches), used quality of life measures, disability assessment, or nonstandardized outcomes as primary efficacy endpoints, or tested the efficacy of drugs not available in the United States.<sup>[7]</sup> After review of pharmacologic agents potentially effective for the prevention of migraine, the AHS/AAN found seven medications that were considered Level A. They are: divalproex, sodium valproate, topiramate, metoprolol, propranolol, timolol, and frovatriptan (for the relief of short term MAM) are recommended for migraine prevention in adults in 2012.

Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy ( $\geq$ 2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs	Antidepressants/SSRI/SSNRI/TCA	ACE inhibitors Lisinopril	Carbonic anhydrase inhibitor	Established as not effective
Divalproex sodium	Amitriptyline	Angiotensin receptor blockers	Acetazolamide	Antiepileptic drugs
Sodium valproate	Venlafaxine	Candesartan	Antithrombotics	Lamotrigine
Topiramate	$\beta$ -Blockers	$\alpha$ -Agonists	Acenocoumarol	Probably not effective
$\beta$ -Blockers	Atenolol <sup>a</sup>	Clonidine <sup>a</sup>	Coumadin	Clomipramine <sup>a</sup>
Metoprolol	Nadolol <sup>a</sup>	Guanfacine <sup>a</sup>	Picotamide	Possibly not effective
Propranolol	Triptans (MRM <sup>b</sup> )	Antiepileptic drugs	Antidepressants SSRI/SSNRI	Acebutolol <sup>a</sup>
Timolol <sup>a</sup>	Naratriptan <sup>b</sup>	Carbamazepine <sup>a</sup>	Fluvoxamine <sup>a</sup>	Clonazepam <sup>a</sup>
Triptans (MRM <sup>b</sup> )	Zolmitriptan <sup>b</sup>	$\beta$ -Blockers	Fluoxetine	Nabumetone <sup>a</sup>
Frovatriptan <sup>b</sup>		Nebivolol	Antiepileptic drugs	Oxcarbazepine
		Pindolol <sup>a</sup>	Gabapentin	Telmisartan
		Antihistamines	TCA	
		Cyproheptadine	Protriptyline <sup>a</sup>	
			$\beta$ -Blockers	
			Bisoprolol <sup>a</sup>	
			Ca++ blockers	
			Nicardipine <sup>a</sup>	
			Nifedipine <sup>a</sup>	
			Nimodipine	
			Verapamil	
			Direct vascular smooth muscle relaxants	
			Cyclandelate	

Abbreviations: ACE = angiotensin-converting-enzyme; MRM = menstrually related migraine; SSNRI = selective serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

<sup>a</sup> Classification based on original guideline and new evidence not found for this report.

<sup>b</sup> For short-term prophylaxis of MRM.

### III. DISCUSSION

Three classes of drugs are represented in the guidelines established by the AHS/ AAP for migraine prevention; antiepileptic drugs (AEDs), beta-blockers and triptans. Antiepileptic drugs (AEDs) clinicians should consider as potentially effective medications in the prevention of migraine are divalproex sodium, sodium valproate, and topiramate. Beta-blockers that clinicians should consider as potentially effective medications in the prevention of migraine are metoprolol, propranolol, and timolol. For short-term migraines associated with menstruation (MAM), the triptan frovatriptan should be considered.<sup>[7]</sup>

### IV. SUMMARY

Preventative treatment of migraine is an important part of migraine management. The goal of preventative therapy is to reduce frequency, pain, and/or duration of migraine headache and increase the effectiveness of abortive therapy. After a retrospective review of 284 articles from 2000-2012, the AAN/AHS updated their 2000 pharmacologic treatment guidelines. According to the recent findings of the AAN/ANH, divalproex, sodium valproate, topiramate, metoprolol, propranolol, timolol, and frovatriptan (for the relief of short term MAM) are recommended for migraine prevention in adults in 2012.

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