UNDERSTANDING THE PATHOPHYSIOLOGY IN MIGRAINE TREATMENT AND PREVENTION

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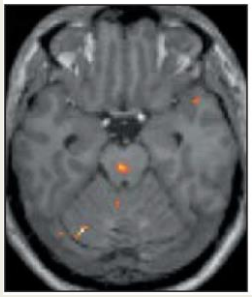
Pathophysiology of Migraine

Triggers

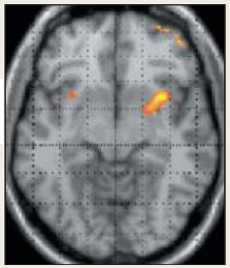
Dysfunction of brainstem centers important in regulating vascular tone and pain sensation



dilation of cranial blood vessels that are innervated by sensory fibers of the trigeminal nerve

mechanically activate perivascular **trigeminal sensory nerve fibers**

Higher brain centers



Release of **vasoactive peptides** such as substance P and CGRP from trigeminal fibers.

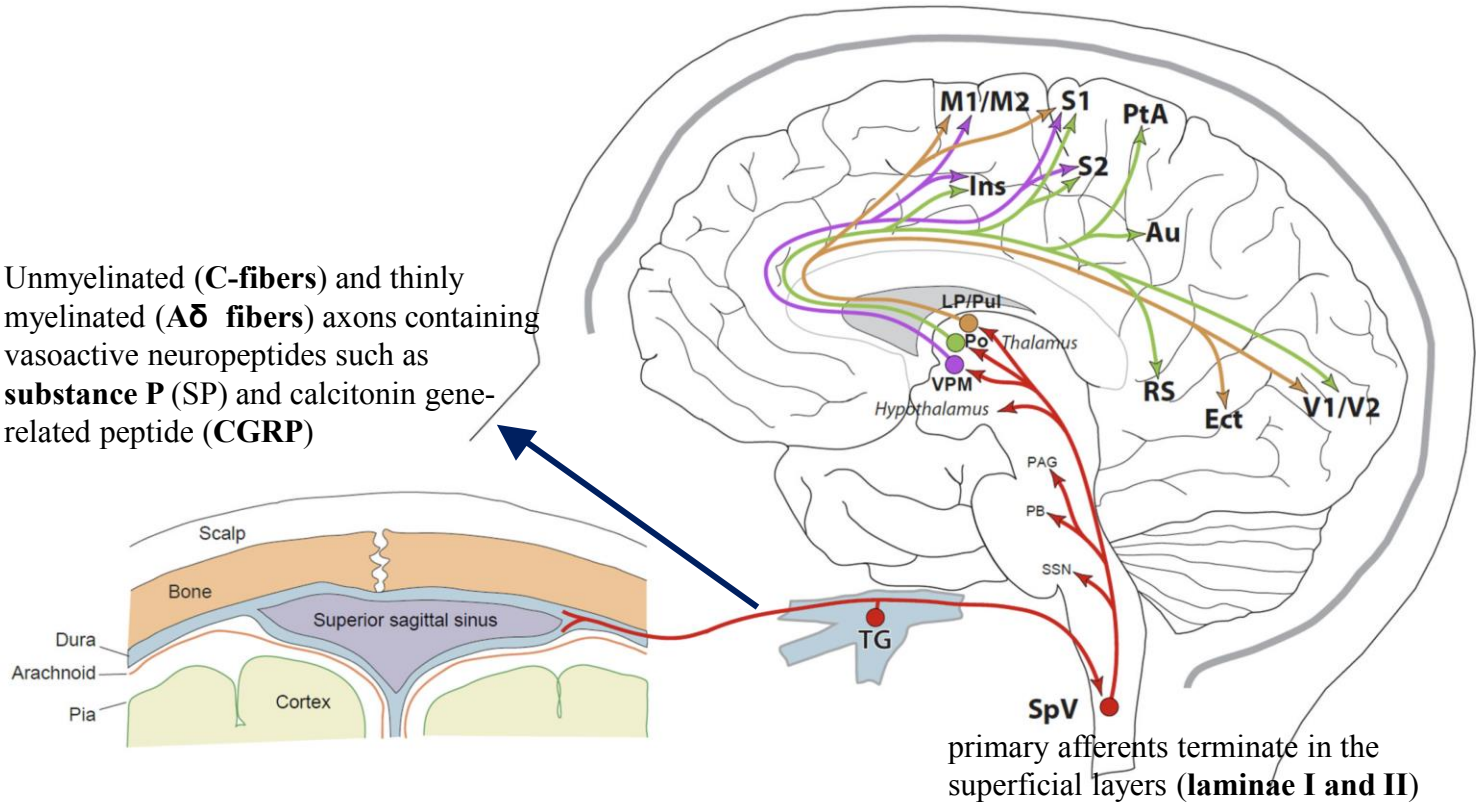
Exacerbate vasodilation cause **neurogenic inflammation** (vasodilation, leakage of blood vessels, and degranulation of mast cells)

Positive feedback and worsening of headache pain and increased sensitivity to stimuli

Headache . 2006 June ; 46(Suppl 1): S3–S8.

Anatomical Pathophysiology

Unmyelinated (**C-fibers**) and thinly myelinated (**Aδ fibers**) axons containing vasoactive neuropeptides such as **substance P** (SP) and calcitonin gene-related peptide (**CGRP**)



primary afferents terminate in the superficial layers (**laminae I and II**)

Figure 1.
Schematic representation of ascending neuronal pathways of the trigeminovascular system that are involved in the different aspects of migraine.

Pain. 2013 Dec;154 Suppl 1:S44-53.

Anatomical Pathophysiology

VPM dura-sensitive neurons → **Primary and secondary somatosensory (S1/S2)** : sensory-discriminative components of migraine such as location, intensity, and quality of pain

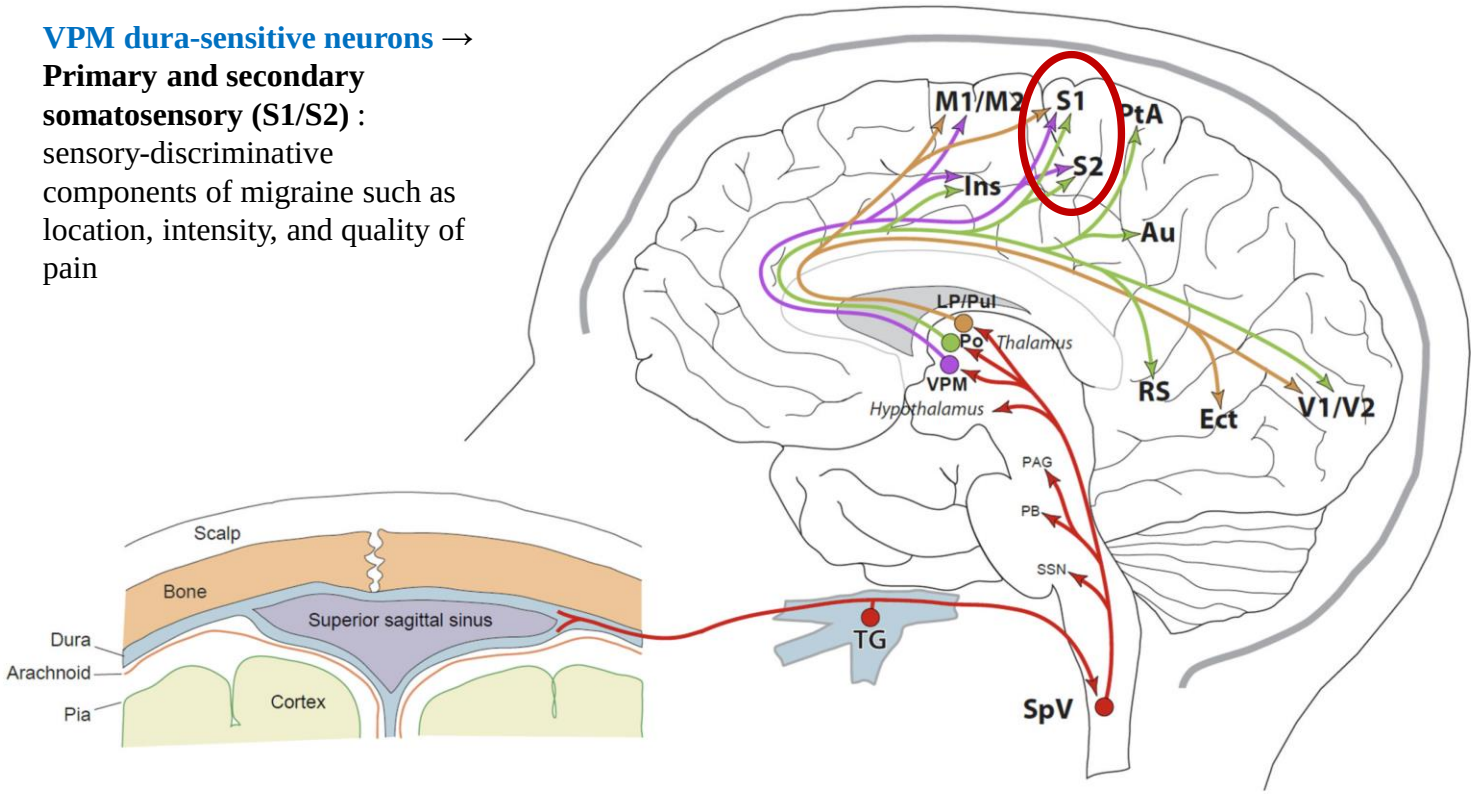
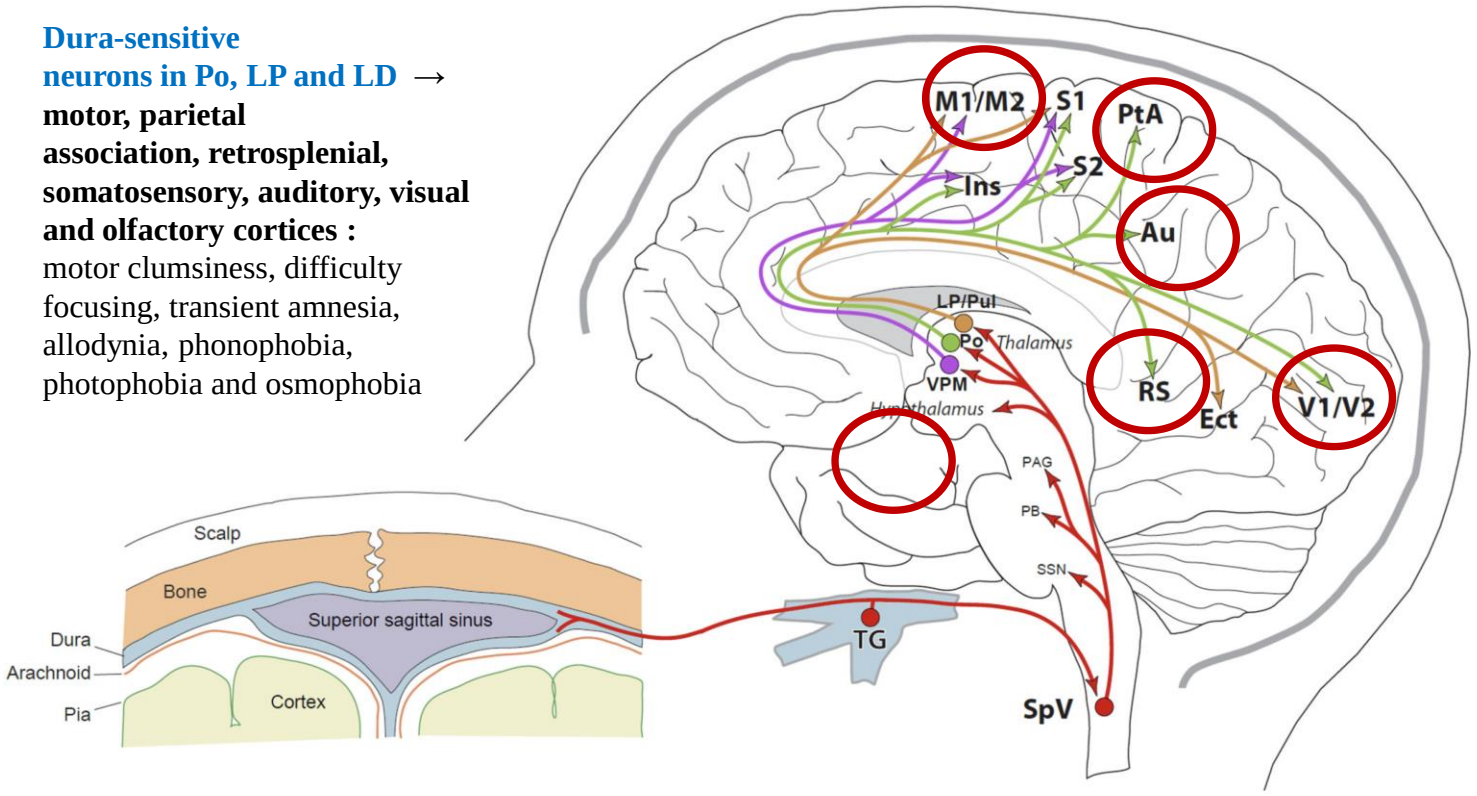


Figure 1.
Schematic representation of ascending neuronal pathways of the trigeminovascular system that are involved in the different aspects of migraine.

Pain. 2013 Dec;154 Suppl 1:S44-53.

Anatomical Pathophysiology

Dura-sensitive neurons in Po, LP and LD → **motor, parietal association, retrosplenial, somatosensory, auditory, visual and olfactory cortices :** motor clumsiness, difficulty focusing, transient amnesia, allodynia, phonophobia, photophobia and osmophobia



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Schematic representation of ascending neuronal pathways of the trigeminovascular system that are involved in the different aspects of migraine.

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CGRP and Migraine

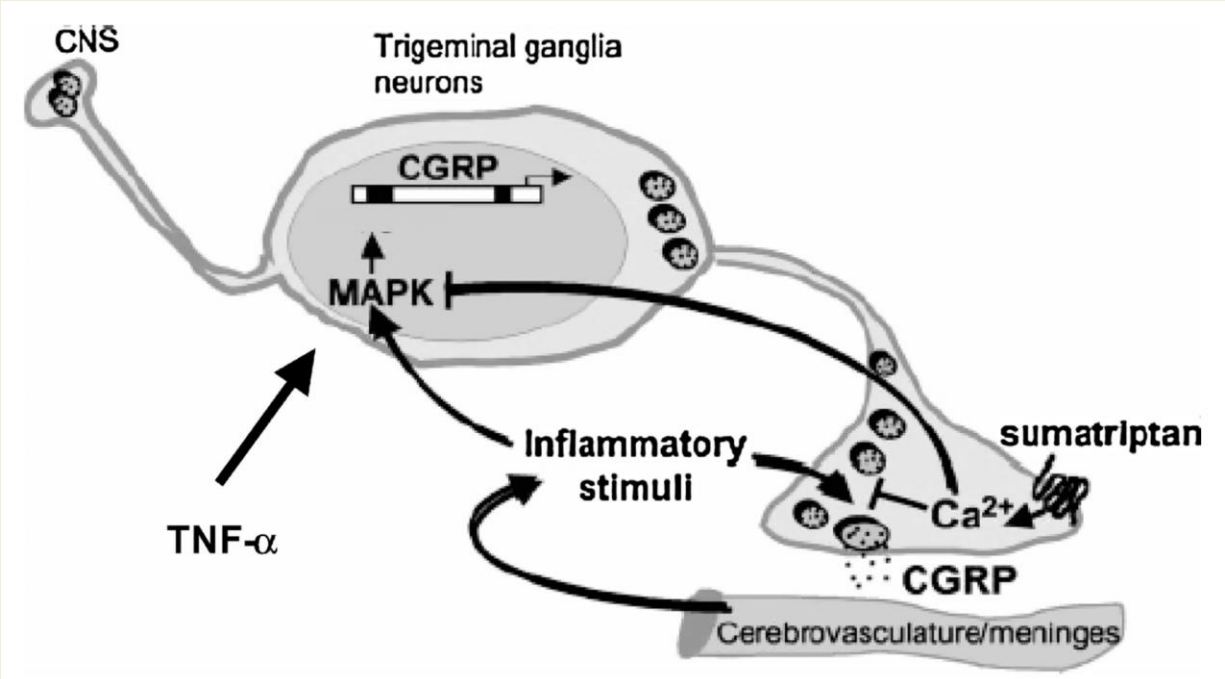


Fig 3.
CGRP regulation in trigeminal ganglia neurons.[14] Activation of trigeminal nerves causes initial release of CGRP and other neuropeptides that promote release of inflammatory mediators. The inflammatory mediators, including TNF-α, further increase CGRP synthesis and release via MAPKs. Sumatriptan can block MAPK activation by causing sustained elevation of intracellular calcium. CNS = central nervous system. (Reproduced with permission from Durham PL, Russo AF. Regulation of calcitonin gene-related peptide secretion by a serotonergic antimigraine drug. *J Neurosci*. 1999;19:3423–3429).

Headache . 2006 June ; 46(Suppl 1): S3–S8.

Treatment approaches

- **Lifestyle and Trigger management**
- **Acute treatments** (i.e. those taken during attacks or exacerbations of chronic pain)
- **Preventive treatments** (medication or other interventions designed to reduce the tendency to have attacks)

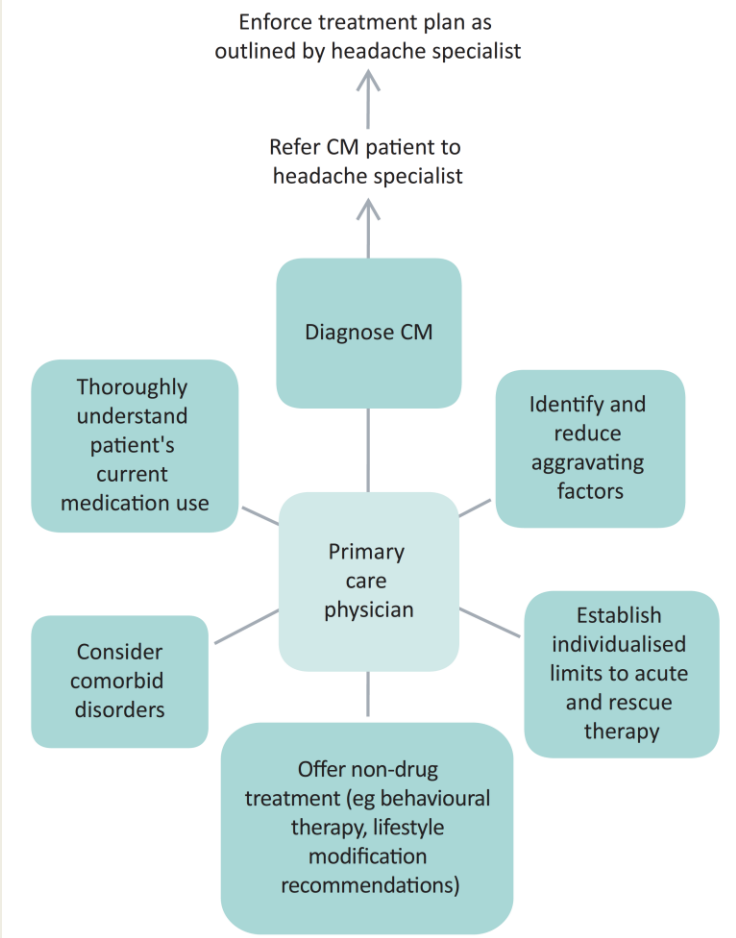


Fig 1. Primary care and the hospital-based physician's role in CM management. CM = chronic migraine.

Clinical Medicine 2015 Vol 15, No 4: 344–50

Ther Adv Chronic Dis 2015, Vol. 6(3) 115–123

Acute headache treatments

Table 1. US Trade Names for Generic Drugs Used in Emergency Room Management of Acute Migraine

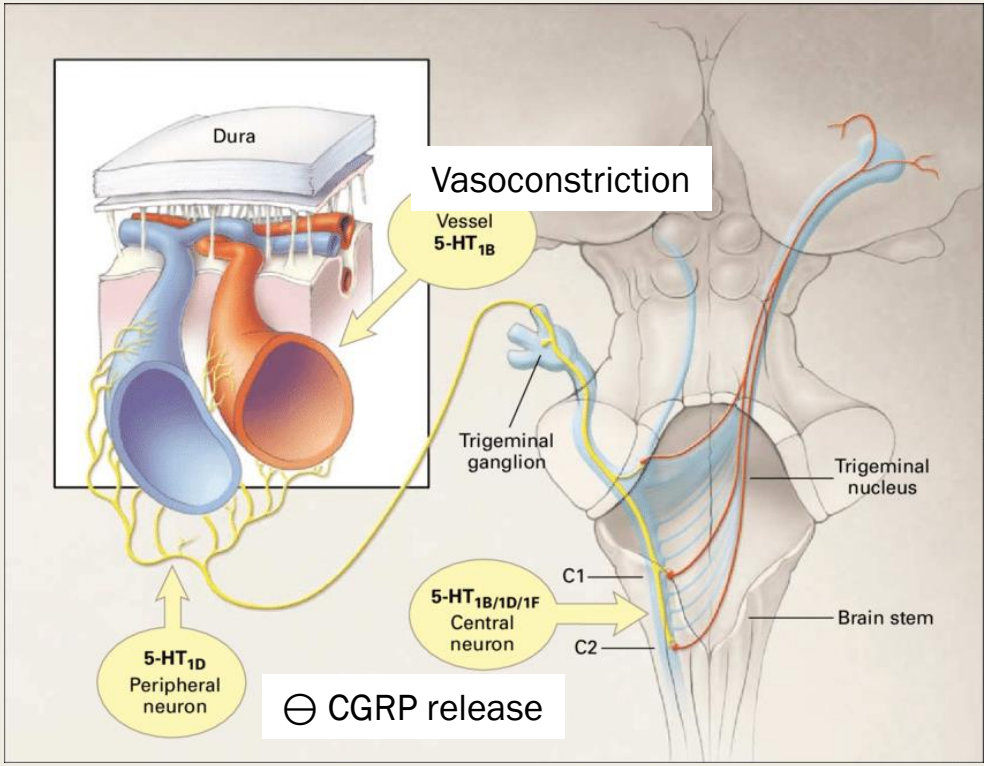
Class of Medication	Generic Drug Name	US Trade Name
Opioids	Meperidine (for example)	Demerol
Dopamine-receptor antagonists	Chlorpromazine	Thorazine
	Prochlorperazine	Compazine
	Promethazine	Phenergan
	Droperidol	Inapsine
	Haloperidol	Haldol
	Metoclopramide	Reglan
Triptans	Sumatriptan	Imitrex
	Zolmitriptan	Zomig
NSAIDs	Ketorolac	Toradol
	Diclofenac	Cataflam, Cambria Votarensodi
Corticosteroids	Dexamethasone	Decadron
Antiepileptics	Sodium valproate	Depacon

Neurohospitalist. 2012 Apr; 2(2): 51–59.

Acute headache treatments
Triptans

Sumatriptan, Zolmitriptan

- $5HT_{1B/1D}$ agonists → directly inhibit CGRP release from activated trigeminal neurons
- sustained ↑ in intracellular calcium and → ↑ in phosphatase activity → inhibit CGRP release from activated trigeminal neurons



Headache. 2006 June ; 46(Suppl 1): S3–S8.

Acute headache treatments
Dopamine receptor antagonists

Metoclopramide, Chlorpromazine, Prochlorperazine

- Dopamine D2 receptor antagonist
- Hypersensitivity to dopamine in migraineurs is thought to play a role in premonitory migraine symptoms such as yawning, nausea, and vomiting

Neurohospitalist. 2012 Apr; 2(2): 51–59.

Acute headache treatments
Corticosteroids

Dexamethasone

- anti-inflammatory effect on neurogenic inflammation
- reduction of vasogenic edema and effects on central aminergic /serotonergic systems

Arq. Neuro-Psiquiatr. vol.59 no.3B São Paulo Sept. 2001

Acute headache treatments
Dihydroergotamine

Mechanism of actions

- 5-$HT_{1B/1D}$ agonist
- 5-HT_{1A} and 5-HT_2 , alpha-1 and -2 adrenergic receptors activity
- DHE binding to the α_2-adrenergic receptor blocks ATP-sensitized trigeminal neurons by decreasing membrane expression of the $P2X_3$receptor protein → ↓ in primary nociception, hyperalgesia, and CGRP release.
- DHE may also be more penetrant of the blood–brain barrier than triptans.

Roger K. Cady, Kathleen Farmer, in Headache and Migraine biology and management, 2015

Preventive treatment

- Considered when
  - *headache frequency or severity increases to a point when it is significantly interfering with work, school or social life.*
  - *For patients with chronic migraine*

Preventive treatment

Table 1.—AHS/AAN Migraine Prevention Guidelines
Drugs Recommended for Use

Drug
Level A: established as effective
Should be offered to patients requiring migraine prophylaxis
Divalproex/sodium valproate
Metoprolol
Petasites (butterbur)
Propranolol
Timolol
Topiramate
Level B: probably effective
Should be considered for patients requiring migraine prophylaxis
Amitriptyline
Fenoprofen
Feverfew
Histamine
Ibuprofen
Ketoprofen
Magnesium
Naproxen/naproxen sodium
Riboflavin
Venlafaxine
Atenolol
Level C: possibly effective
May be considered for patients requiring migraine prophylaxis
Candesartan
Carbamazepine
Clonidine
Guanfacine
Lisinopril
Nebivolol
Pindolol
Flurbiprofen
Mefenamic acid
Coenzyme Q10
Cyproheptadine

Table 2. Recommended preventive treatment in episodic and chronic migraine.[54–66]

Episodic migraine	Chronic migraine
Antiepileptic drugs	Antiepileptic drugs
– Valproate	– Topiramate
– Topiramate +Divalproex sodium	
Antidepressants	Botulinum toxins
– Amitriptyline[a]	– OnabotulinumtoxinA (BOTOX®)
Beta-blockers	
– Metoprolol	
– Propranolol	
Calcium channel blocker	
– Flunarizine	

Headache 2012;52:930-945

Clinical Medicine 2015 Vol 15, No 4: 344–50

Preventive treatment
Beta blocker

Metoprolol(beta-1 selective**), Timolol, Propranolol**

- diminishes central catecholaminergic activity by inhibiting norepinephrine release
- reduces neuronal activity and excitability
- membrane-stabilizing properties, and inhibits nitric oxide production
- Propranolol is highly lipophilic which gives easy access into the central nervous system (CNS) and therefore has a higher potential for CNS side-effects such as depression

Neuropsychiatr Dis Treat. 2006 Sep; 2(3): 281–291.

Preventive treatment
Calcium channel blocker

Flunarizine

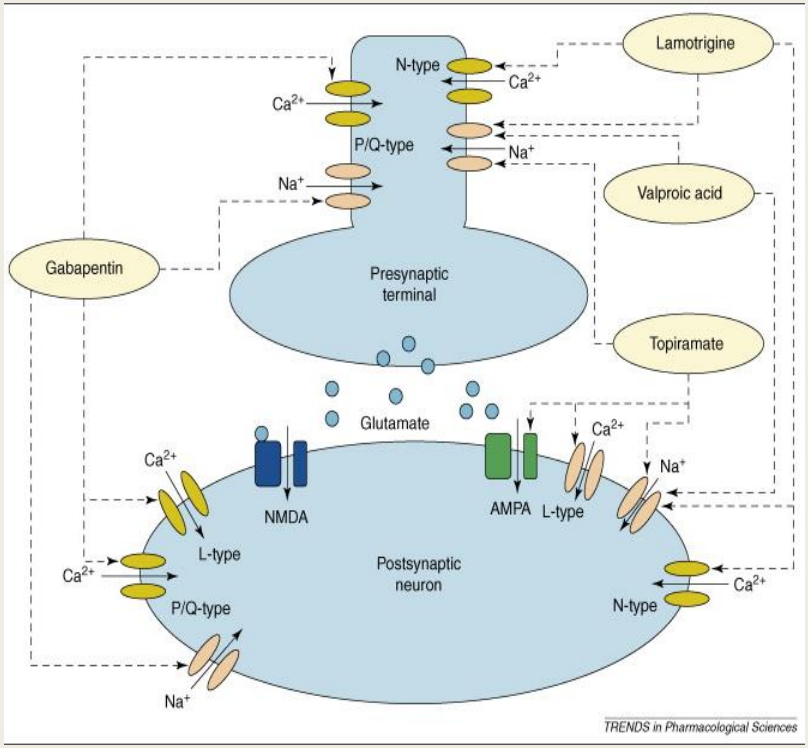
- decreases calcium influx resulting in decreased activity of neural nitric oxide synthase → vasoactive neuropeptide release inhibition and protection against neurogenic inflammation elicited by trigeminal nerve activation

Neuropsychiatr Dis Treat. 2006 Sep; 2(3): 281–291.

Preventive treatment
Antiepileptics

Divalproex sodium

- highly protein-bound fatty acid
- increased GABA which may attenuate migraine-related events at different levels including the cortex, perivascular parasympathetics or trigeminal nucleus caudalis (TNC)
- lowered aspartate levels and NMDA receptor activity resulting in attenuated aura related cortical activity or nociceptive transmission through the TNC
- diminished neurogenic inflammation



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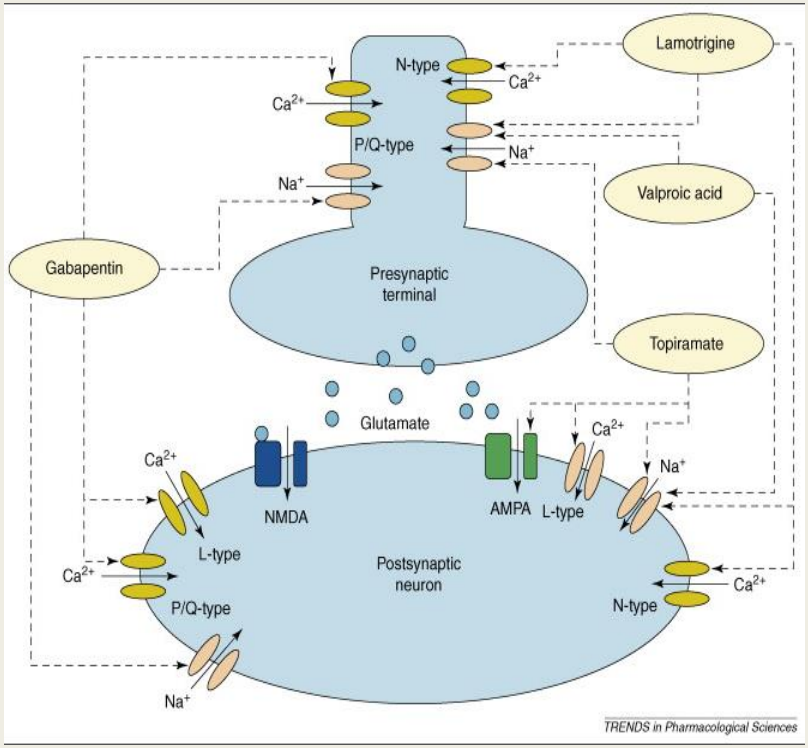
Preventive treatment
Antiepileptics

Topiramate

- D-fructose derivative containing a sulfamate functionality that readily enters the CNS
- phosphorylation-mediated inhibition of voltage gated sodium and calcium channels
- suppression of glutamate-mediated neurotransmission at the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)–kainate receptor subtype
- enhanced GABA type A activity
- calcium channel (subtypes L and N) blockade

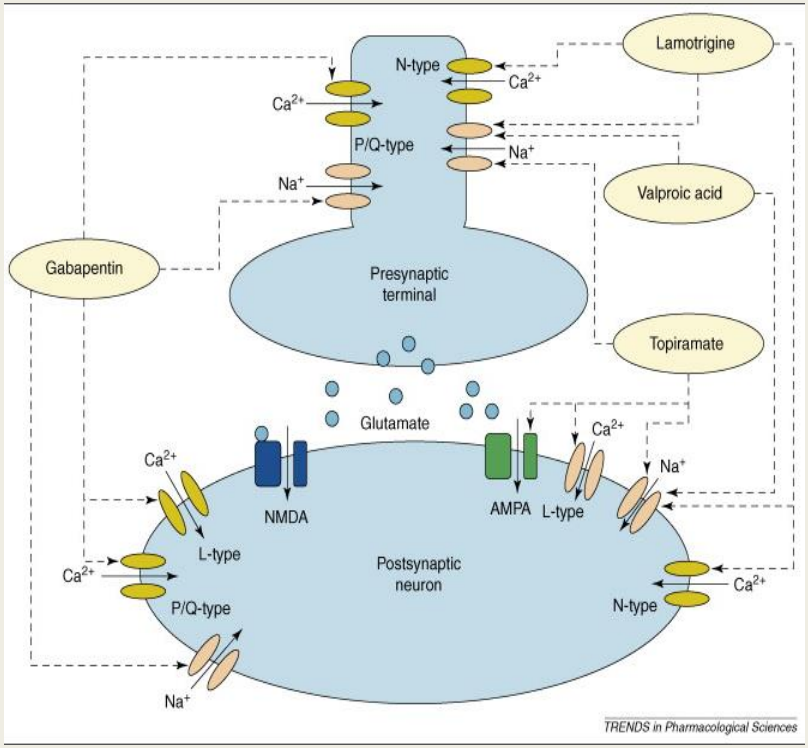


Neuropsychiatr Dis Treat. 2006 Sep; 2(3): 281–291.

Preventive treatment
Antiepileptics

Valproate

- potentiates gamma-aminobutyric acid (GABA)
- decreases the activation in the trigeminal nucleus



Neurohospitalist. 2012 Apr; 2(2): 51–59.

Preventive treatment
Tricyclic antidepressants

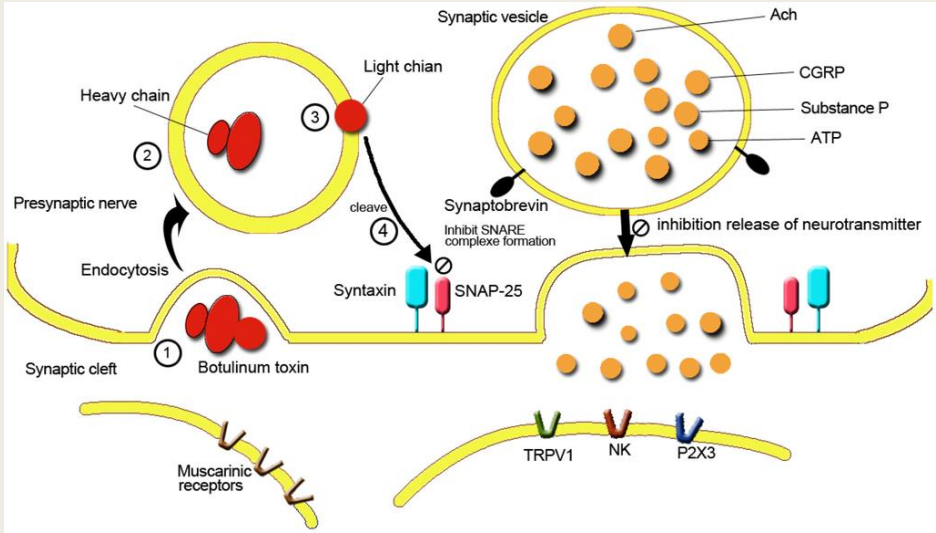
Amitriptyline

- lipid-soluble and strongly bind to plasma proteins.
- inhibits norepinephrine and serotonin uptake
- Other : ability to block sodium-channels; enhance GABA-mediated inhibition; potentiate endogenous opioids; and intensify descending inhibition on nociceptive pathway
- Antimigraine effects seem to be independent of its antidepressant influence

Neurohospitalist. 2012 Apr; 2(2): 51–59.

Preventive treatment
Botulinum toxin type A

- local injection
- unlike triptans, is not a 5HT1 agonist
- inhibit release of CGRP from trigeminal sensory neurons stimulated with potassium chloride or capsaicin
- Does not affect CGRP release from unstimulated trigeminal sensory neurons.



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Preventive treatment
CGRP receptor antagonists

- non-peptide CGRP receptor antagonists **olcegepant** and **telcagepant**
- CGRP receptor antagonists in the acute treatment of migraine likely involves repressing the function of cells located in peripheral tissues as well as in the CNS
- **olcegepant** was clinically not further pursued, because of poor oral bioavailability, and **telcagepant** revealed some liver toxicity indicated by elevated transaminases when it was given daily to test its prophylactic use or to prevent menstrual migraine

J Headache Pain. 2018; 19(1): 3.

CNS Drugs. 2010 Jul 1; 24(7): 539–548.

Preventive treatment
CGRP receptor antagonists

Location	Cell Type	Proposed Function of CGRP Antagonist Binding
Dura	Smooth muscle cells	Block vasodilation of meningeal vessels, decrease inflammatory response
Dura	Mast cells	Prevent mast cell activation and secretion of vasoactive, inflammatory, and sensitizing molecules (Lennerz et al., 2008)
Trigeminal ganglion (TG)	Neurons	Suppress sensitization of primary afferents
TG	Satellite glia	Repress sensitization and activation of primary nociceptive neurons
Trigeminal nucleus caudalis(TNC)	Neurons	Inhibit sensitization of second order neurons (Williamson et al., 2001)

CNS Drugs. 2010 Jul 1; 24(7): 539–548.

Preventive treatment
Fremanezumab

- Humanized IgG2a monoclonal antibody that selectively and potently binds to calcitonin gene–related peptide (CGRP) → Scavenging CGRP
- Targets both α and β isoforms of the CGRP ligand (not the receptor)
- Flexible dosing
- Subcutaneous injection
- No serious treatment-related adverse events

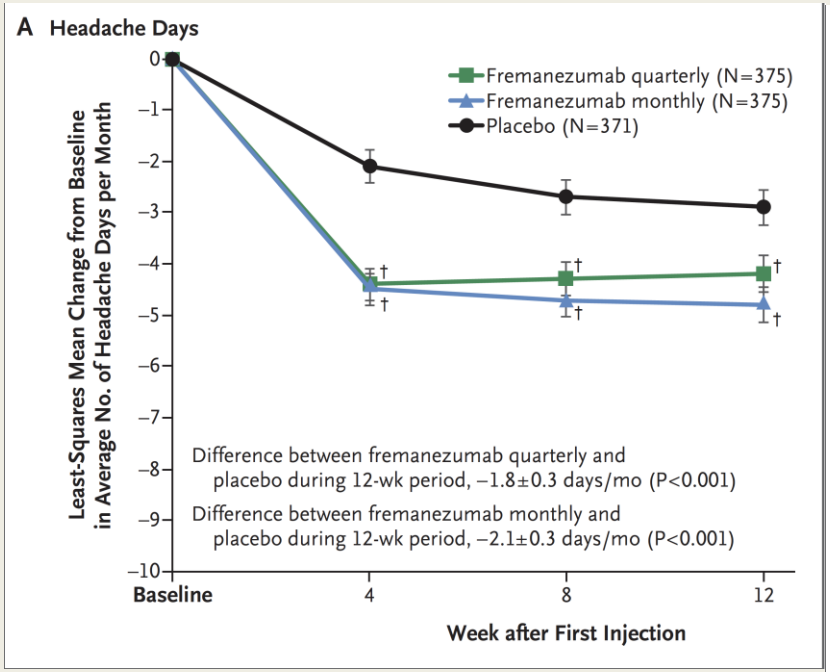
N Engl J Med 2017; 377:2113-2122

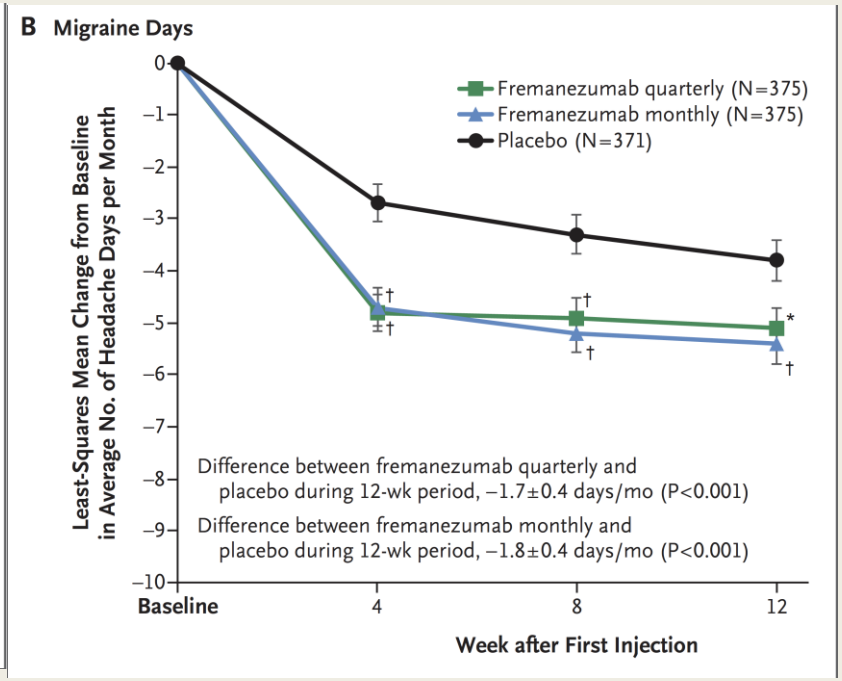
Preventive treatment

Fremanezumab

Primary end point : mean change in the average number of headache days (days in which headache pain lasted ≥4 consecutive hours

Secondary end points : mean change from baseline in the average number of migraine days per month





fremanezumab-quarterly group : single dose of 675 mg of fremanezumab at baseline (three injections of 225 mg per 1.5 ml) + followed at weeks 4 and 8 by placebo (one 1.5-ml injection)
fremanezumab-monthly group : 675 mg of fremanezumab at baseline (as above) + 225 mg of fremanezumab at weeks 4 and 8 (one injection of 225 mg per 1.5 ml)

N Engl J Med 2017; 377:2113-2122

Reference for additional images

- DOI: https://doi.org/10.1016/j.tips.2007.02.005
- New England Journal of Medicine 346(4):257-70
- *Toxins* **2015**, *7*(6), 2232-2250