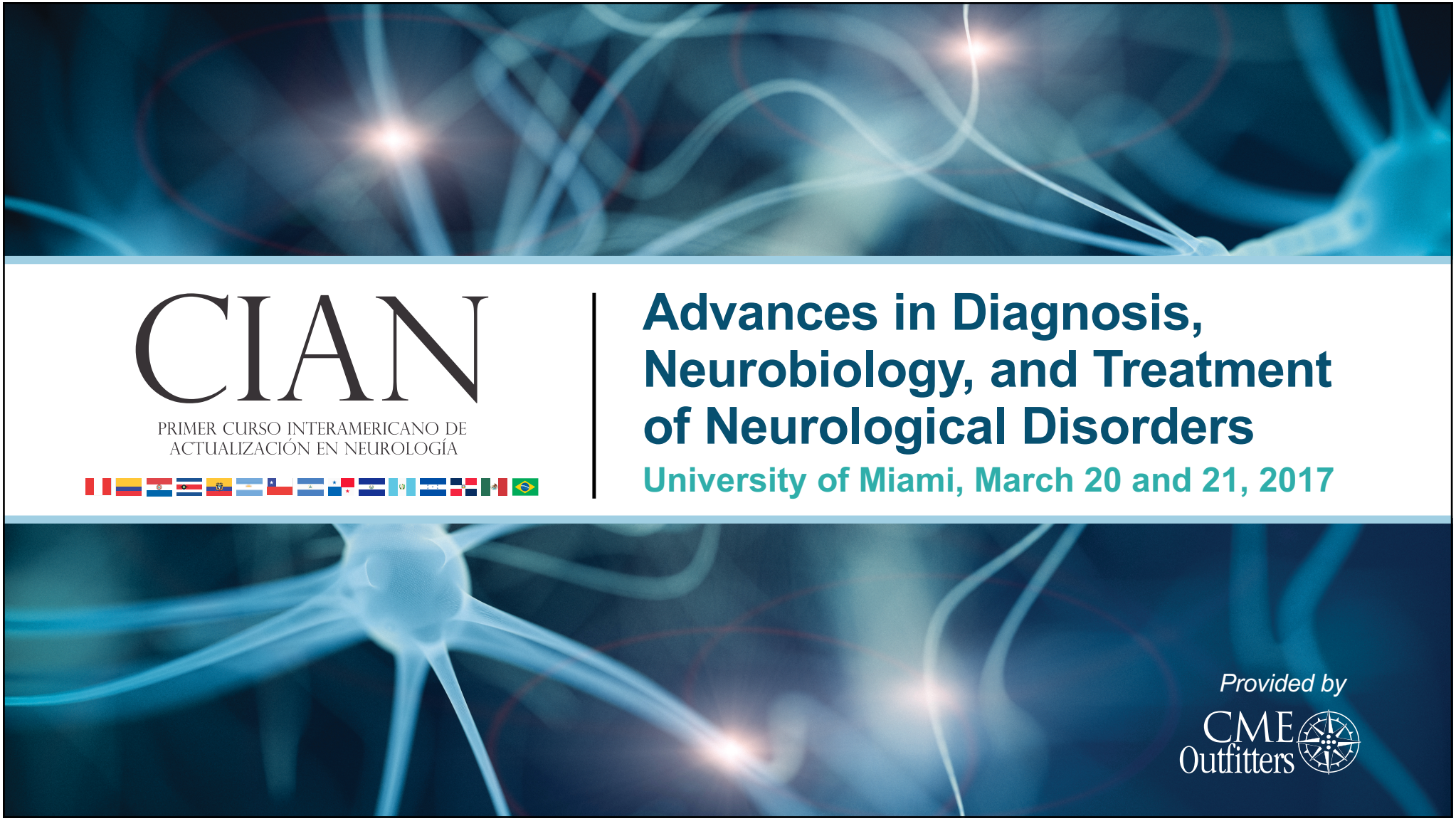

CIAN

PRIMER CURSO INTERAMERICANO DE ACTUALIZACIÓN EN NEUROLOGÍA

Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

University of Miami, March 20 and 21, 2017

Provided by

CME Outfitters

Teshamae Monteith, MD, FAHS

University of Miami
Miller School of Medicine
Miami, FL

Teshamae Monteith, MD, FAHS

Disclosures

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- ***Other Financial or Material Support***: Received travel funds from Teva
- ***Consulting***: Supernus, Eli Lilly

What's New in Migraine Prevention and Treatment

Learning Objective 1

Identify clinical signs and symptoms that will lead to the early recognition and accurate diagnosis of migraine.

Learning Objective 2

Describe the latest evidence for current therapies/technologies as part of an individualized multimodal migraine management plan.

Migraine is a Major Public Health Problem

Global burden of disease (2010)

- Migraine is the 3rd most common medical condition worldwide
- 4th most disabling condition among women
- Migraine accounts for > 50% of the disability burden attributable to all neurological disease worldwide[1]

American Migraine Prevalence and Prevention Study

- Among 8233 eligible respondents with episodic migraine, 56.0% of respondents reported inadequate 2h pain response to usual acute treatment and 53.7% reported inadequate 24 hour pain relief[2]

1. Murray CJ, et al. *Lancet.* 2012;380:2197-223.
2. Lipton RB, et al. *Headache.* 2016;56(10):1635-1648.

Diagnosis of Migraine

A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

*Chronic migraine (CM) defined as > 15 headache days/month, 8 migraine days (for over 3 months)

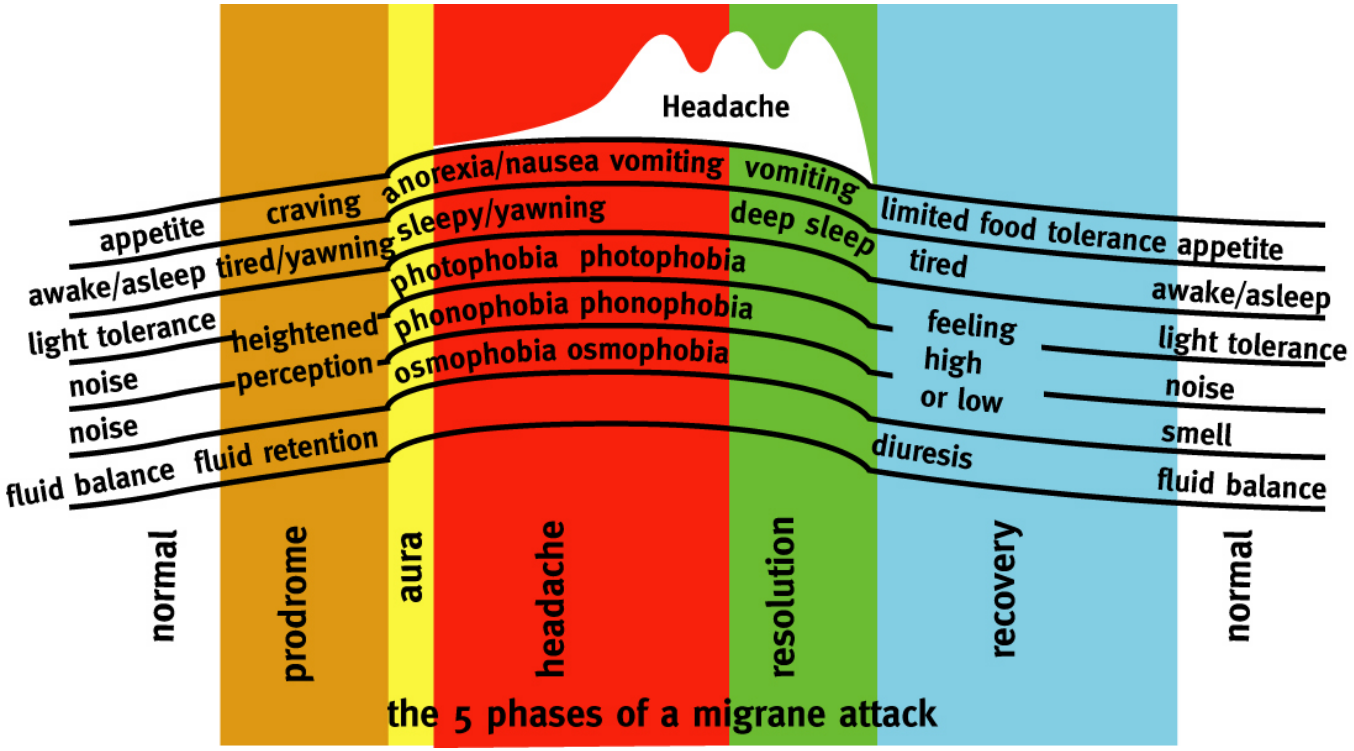
Rizzoli P, et al. The Migraine Solution: A Complete Guide to Diagnosis, Treatment, and Pain Management. Harvard University. St Martin's Press, New York, NY. 2012.

ICHD-3 Beta Migraine Classification

- Migraine without aura
- Migraine with aura
- Migraine with typical aura
- Typical aura without headache
- Migraine with brainstem aura
- Hemiplegic migraine (1-3)
- Sporadic hemiplegic migraine
- Retinal migraine
- Chronic migraine (+aura)
- Complications of migraine
- Complications of migraine
  - Status migrainous
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- Probable migraine: with, without aura
- Episodic syndromes
  - Recurrent GI disturbance
  - Cyclical vomiting syndrome
  - Abdominal migraine
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis

International Headache Society. International Classification of Headache Disorders. Third Edition 2013.

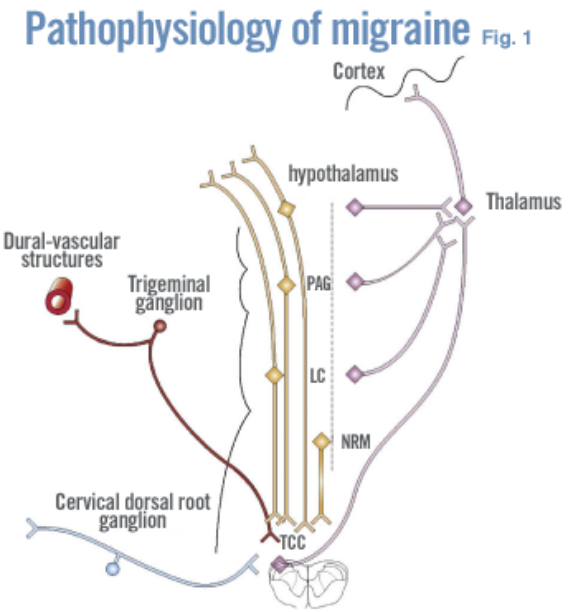
Migraine Phases



Migrainetalkblog @ https://migrainetalkblog.wordpress.com/2014/09/14/the-5-possible-stages-of-a-migraine-attack-2/. Published September 14, 2014. Accessed March 8, 2017.

Major Structures in the Activation of Trigeminovascular System

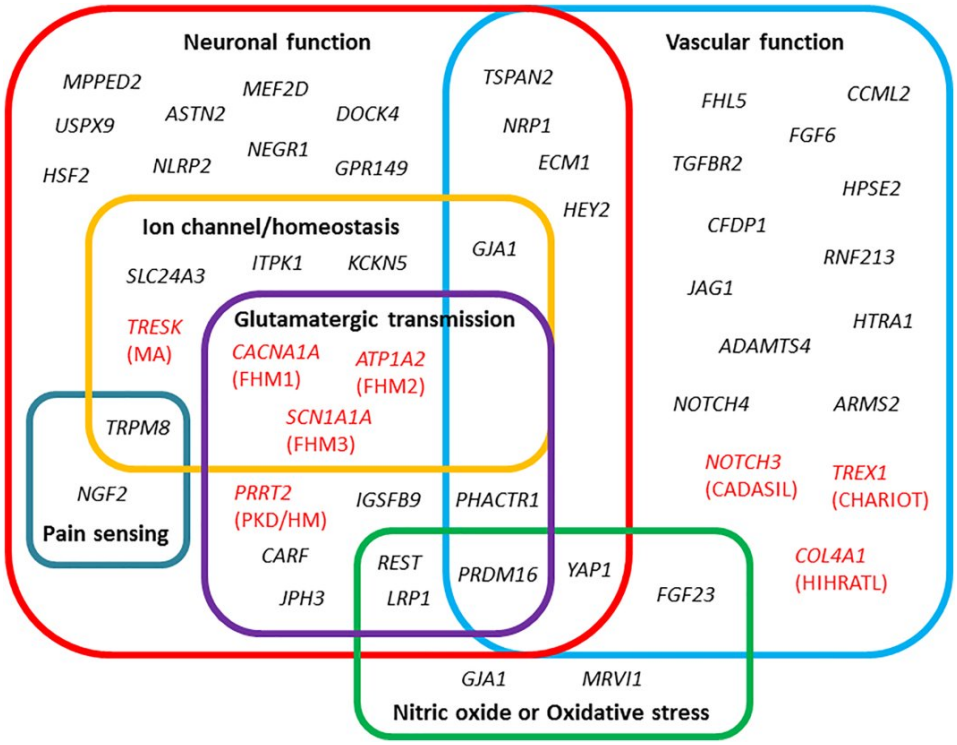
- Sensory neurons from the trigeminal ganglion and upper cervical dorsal roots innervate dural-vascular structures (eg, pial vessels, dura mater, large cerebral vessels).
- Input from dural-vascular structures and from cervical structures through the upper cervical dorsal root ganglia project to second order neurons in the trigeminocervical complex (TCC).
- Second-order neurons of the TCC project to the posterior thalamus.
- Distribution of headache pain to regions of the upper neck and head can be attributed to the convergence of projections from the trigeminal nerve at the trigeminal nucleus caudalis and upper cervical nerve roots.
- The sphenopalatine ganglion (SPG) also provides reflex parasympathetic innervation to dural vessels. Interestingly, the SPG and nerves contain PACAP and its receptors.



Periaqueductal gray = PAG; pontine locus coruleus = LC; nucleus raphe magnus = NRM.
Reproduced from Goadsby PJ. *Neurol Clin*. 2009;27:335-60.

Migraine Genetics: Molecular Basis of Migraine

MwO, MA, FHM

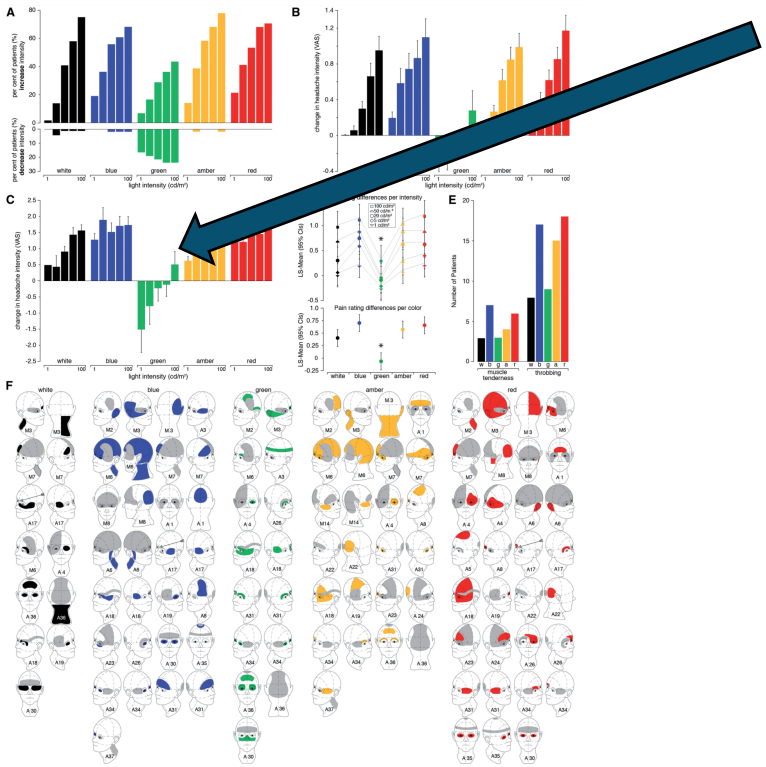


Molecular Genetic Testing Used in Familial Hemiplegic Migraine (FHM)

Gene (Locus Name)	Proportion of FHM Attributed to Mutation of This Gene	Test Method
CACNA1A (FHM1)	3/42 (7%)	Sequence analysis
		Gene-targeted, deletion/duplication analysis
ATP1A2 (FHM2)	3/42 (7%)	Sequence analysis
SCN1A (FHM3)	Unknown	Sequence analysis
		Gene-targeted, deletion/duplication analysis
Unknown	Unknown	NA

Jen JC. In: Pagon RA, et al, editors. *GeneReviews*®: University of Washington, Seattle; 1993-2017.
Sutherland H G, Griffiths LR. *Headache: The Journal of Head and Face Pain*. 2017. doi: 10.1111/head.13053.

Photophobia and Effects of Color on Pain Ratings, Throbbing, Muscle Tenderness and Headache Location



(A) Each light stimulus presented for 30 s at low (1 and 5 cd·m $^{-2}$) and medium (20, 50 and 100 cd·m $^{-2}$) intensities.

(B) Numerical change in headache intensity (mean ± SEM) reported by all patients in response to each color and intensity (VAS = verbal analogue scale).

(C) Bar graphs showing only those trials in which lights altered pain perception. *Note that all colors but green increased pain ratings by a maximum of 15–20%* (0–10 VAS), *whereas green—the only color to decrease pain ratings—attenuated* the pain by a maximum of 15%.

Brain. 2016;139(7):1971-1986. doi:10.1093/brain/aww119.

Goals of Preventive Care

- Maintain high quality of life and little to no headache related impact
- Minimize emergency room and urgent care visits
- Limit medication overuse and risk of acute medications side effects
- Minimal or no adverse side effects immediate or long term
- Cost effective, patient preferences, characteristics and side effect profiles

ANNALS OF MEDICINE JANUARY 23, 2017 ISSUE

THE HEROISM OF INCREMENTAL CARE

We devote vast resources to intensive, one-off procedures, while starving the kind of steady, intimate care that often helps people more.

By Atul Gawande

By 2010, Bill Haynes had spent almost four decades under attack from the inside of his skull. He was fifty-seven years old, and he suffered from severe migraines that felt as if a drill were working behind his eyes, across his forehead, and down the back of his head and neck. They left him nauseated, causing him to vomit every half hour for up to eighteen hours. He'd spend a day and a half in bed, and then another day stumbling through sentences. The pain would gradually subside, but often not entirely. And after a few days a new attack would begin.

Gawande A. http://www.newyorker.com/magazine/2017/01/23/the-heroism-of-incremental-care. January 23, 2017.

Migraine and Patient Satisfaction

- Migraine specific medication is associated with the highest acute medication satisfaction and lowest disability when taken during mild pain as compared with opiates and bultabital[1]
- Preferred education included timing, coadministration of other drugs, and side effects[2]
- In chronic migraine patients, the satisfaction with acute medications is 48%.[3]
- Successful preventive treatment requires not only efficacy but acceptable side effects. Acceptable of side effects various with the number of drugs taken. Weight gain, memory loss, and depression were commonly unacceptable.[4]
- According to the AMPP study, persons with anxiety and depression were more likely to have unmet treatment needs.[5]

1.Seng EK, et al. *Cephalalgia*. 2016 Aug 3. [Epub ahead of print] ; 2.Mathew PG, et al. *Headache*. 2014;54(4):698-708; 3.Bigal ME, et al. *Headache*. 2008;48(8):1157-1168; 4.Kowacs PA, et al. *Headache*. 2009;49(7):1022-1027; 5.Lipton RB, et al. *Cephalalgia*. 2013;33(4):223-225.

What's New? Individualized Multimodal Migraine Management Plan

- Requires confirm accurate diagnosis
- Evaluate for lifestyle factors and trigger management
  - Sleep, diet, stress, exercise, menstrual migraine, medication usage
- Occupational factors and disability
- Assess patient satisfaction with medication management
- Evaluate for vascular and psychiatric comorbidities
- Psychosocial factors
  - Relaxation training, biofeedback, & cognitive-behavioral therapy
- Migraine diary
  - Electronic resources

Lacerenza MR, et al. *J Headache Pain*. 2015;16(Suppl 1):A47.

Migraine Assessments and Quality of Life

- Migraine Diary
- Headache Impact Test (HIT-6)
- Migraine Disability Assessment Test (MIDAS)
- Migraine Specific Quality of Life
- Refractory Scale for chronic migraine
- Beck Depression Inventory-II and Hamilton Anxiety Scale
- Pain Catastrophizing Scale
- 36 item short survey (SF-36)
- Epworth Sleepiness Scale

Dowson AJ. *Curr Med Res Opin*. 2001;17(4):298-309.

Identifying Risk Factors for Chronic Migraine

- Head injury
- Snoring
- Caffeine
- Depression
- Allodynia
- Anxiety
- Asthma
- Hypothyroidism
- Insomnia/snoring
- Treatment patterns
- Attack frequency, nausea, allodynia
- Obesity
- Pain Disorder
- Low education /socioeconomic status
- Stressful life events / major life changes

May A, et al. *Nat Rev Neurol*. 2016;12(8):455-464.

AAN Guidelines for Prevention: Level A

Anti-convulsants

- Divalproex/sodium valproate 400-1000 mg/day
- Topiramate 25-200 mg/day

Beta Blockers

- Metoprolol 47.5-200 mg/day
- Propranolol 120-240 mg/day
- Timolol 10-15 mg bid

Loder E, et al. *Headache*. 2012;52(6):930-945.

AAN Guidelines for Prevention: Level B

Antidepressants

- Amitriptyline 25-150 mg/day
- Venlafaxine 150 mg extended release/day

Antihypertensives

- Atenolol 100 mg/day
- Histamine 1-10 ng subcutaneously 2x/week

NSAIDs

- Fenoprofen 200-600 mg tid
- Ibuprofen 200 mg bid
- Ketoprofen 50 mg tid
- Naproxen/naproxen sodium 500-1100 mg/day for naproxen 550 mg bid for naproxen sodium

Loder E, et al. *Headache*. 2012;52(6):930-945

AAN Guidelines for Prevention: Level C

Antihypertensives

- Candesartan 16 mg/day
- Clonidine 0.75-0.15 mg/day; patch formulations also studied
- Lisinopril 10-20 mg/day
- Nebivolol 5 mg/day
- Pindolol 10 mg/day

NSAIDs

- Flurbiprofen 200 mg/day
- Mefenamic acid 500 mg tid
- Cyproheptadine 4 mg/day

Anticonvulsants

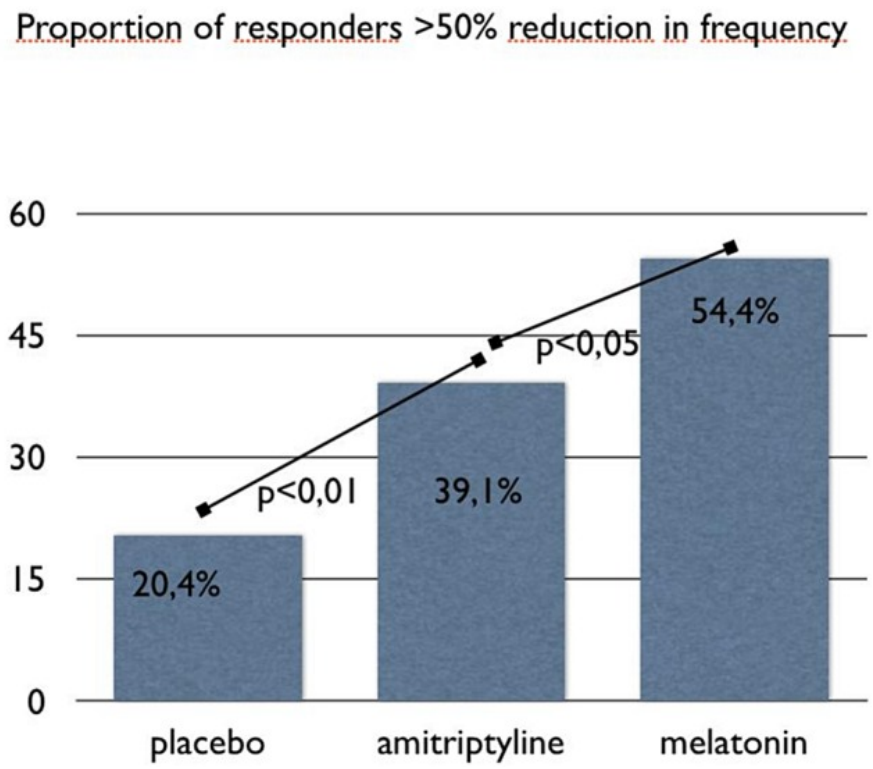
- Carbamazepine 600 mg/day

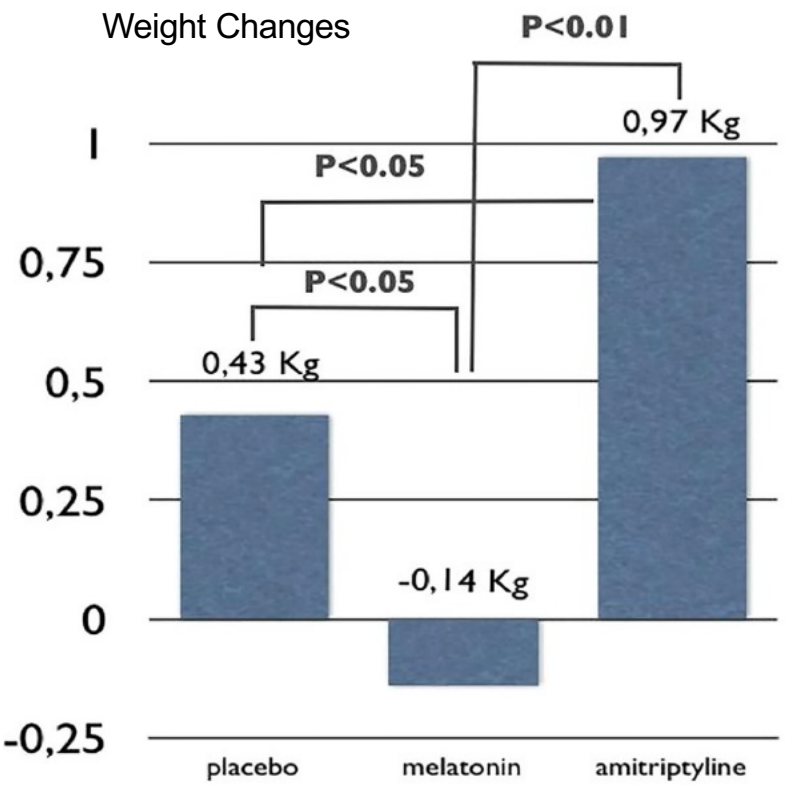
Other

- Guanfacine 0.5-1 mg/day

Loder E, et al. *Headache*. 2012;52(6):930-945

RCT Comparing Melatonin 3 mg vs Amitriptyline 25 mg vs. Placebo





RCT = Randomized controlled trials

Goncalves AL, et al. *J Neurol Neurosurg Psychiatry* 2016;87(10):1127–1132.

Comparative Study of Candesartan vs Propranolol for Migraine Prophylaxis

- Randomized, triple-blind, placebo-controlled double crossover trial
- N = 72 episodic or chronic migraine, 12-wk treatment periods on candesartan (CAN) 16 mg, propranolol (PRO) slow-release 160 mg, or placebo (PBO)
- In modified IIT-analysis, CAN and PRO were both superior to PBO: 2.95 (95% confidence interval: 2.35-3.55%) and 2.91 (2.36-3.45%), versus 3.53 (2.98-4.08%) for migraine days per month (p = .02 for both comparisons)
- The proportion of responders was significantly higher on CAN (43%) and PRO (40%) than PBO (23%) (p = .025 and <.050, respectively).
- More adverse events on CAN (n = 133%) and PRO (n = 143%) than on PBO (n = 90%), and the adverse event profiles of the active substances differed somewhat.

Stovner LJ, et al. *Cephalalgia*. 2014;34(7):523-32.

AHS Guidelines for Acute Medication: Level A

- **Analgesic**
  - Acetaminophen 1000 mg (for non-incapacitating attacks)
- **Ergots**
  - DHE Nasal spray 2 mg, Pulmonary inhaler 1 mg
- **NSAIDs**
  - Aspirin 500 mg, diclofenac 50, 100 mg, Ibuprofen 200, 400 mg, naproxen 500, 550 mg
- **Opioids**
  - Butorphanol nasal spray 1 mg
- **Triptans**
  - Almotriptan 12.5 mg, Eletriptan 20, 40, 80 mg, Frovatriptan 2.5 mg, Naratriptan 1, 2.5 mg, Rizatriptan 5, 10 mg, Sumatriptan Oral 25, 50, 100 mg, Nasal spray 10, 20 mg, Patch 6.5 mg, SC 4, 6 mg, Zolmitriptan nasal spray 2.5, 5 mg, Oral 2.5, 5 mg
- **Combinations**
  - Acetaminophen/aspirin/caffeine 500/500/130 mg, Sumatriptan/naproxen 85/500 mg

Marmura, M, et al. *Headache*. 2015;55(1):3-20.

AHS Guidelines for Acute Medication: Level B

- **Antiemetics**
  - Chlorpromazine IV 12.5 mg, Droperidol IV 2.75 mg, Metoclopramide IV 10 mg
  - Prochlorperazine IV/IM 10 mg; PR 25 mg
- **Ergots**
  - DHE IV, IM, SC 1 mg, Ergotamine/caffeine 1/100 mg
- **NSAIDs**
  - Flurbiprofen 100 mg, Ketoprofen 100 mg, Ketorolac IV/IM 30-60 mg
- **Others**
  - $MgSO_4$ IV (migraine with aura) 1-2 g, Isometheptene 65 mg
- **Combinations**
  - Codeine/acetaminophen 25/400 mg, Tramadol/acetaminophen 75/650 mg

Marmura, M, et al. *Headache*. 2015;55(1):3-20.

AHS Guidelines for Acute Medication: Level C

- **Steroid**
  - Dexamethasone IV 4-16 mg
- **Others**
  - Butalbital 50 mg
  - Lidocaine intranasal
- **Combinations**
  - Butalbital/acetaminophen/caffeine/codeine 50/325/40/30 mg
  - Butalbital/acetaminophen/caffeine 50/325/40 mg
- **Antiepileptic**
  - Valproate IV 400-1000 mg
- **Ergot**
  - Ergotamine 1-2 mg
- **NSAIDs**
  - Phenazone 1000 mg
- **Opioid**
  - Butorphanol IM 2 mg, Codeine 30 mg PO,
  - Meperidine IM 75 mg, Methadone IM 10 mg
  - Tramadol IV 100 mg

Marmura, M, et al. *Headache*. 2015;55(1):3-20.

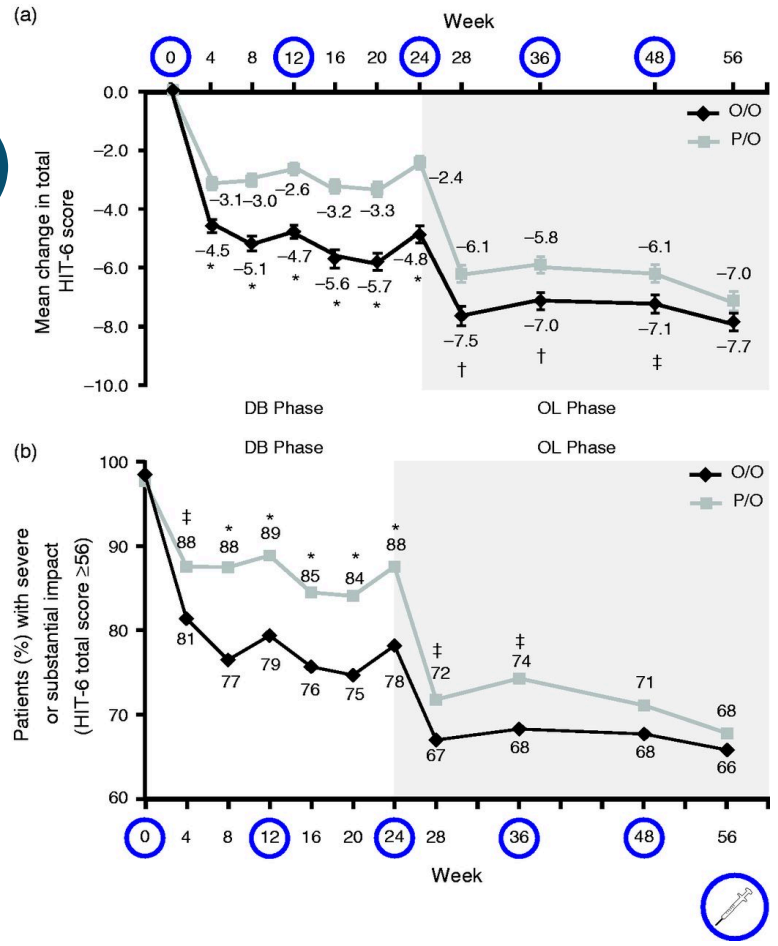
Preventive Pharmacotherapy Evidence for Use in Chronic Migraine

Treatment	Evidence for Use in CM
Anticonvulsants **Topiramate** Gabapentin Valproate	Double-blind placebo-controlled trials in CM One double-blind, placebo-controlled trial in CDH Small placebo-controlled and comparator trials in CM
Antidepressants Amitriptyline Fluoxetine Tizanidine	Small open-label trial in TM Small double-blind, placebo-controlled trial in CDH Small double-blind, placebo-controlled trial in CDH (adjunctive)
Neurotoxins **Onabotulinumtoxin A*** *FDA approved for Chronic Migraine	Double-blind placebo-controlled trials in CM

Estemalik E, et al. *Neuropsychiatr Dis Treat*. 2013;9:709-720.

Efficacy of Onabotulinum Toxin A for Chronic Migraine with a Severe Headache Impact (HIT-6)

Efficacy of onabotulinum toxin A vs. placebo on changes in (a) mean change (standard error) in total HIT-6 score a and (b) percentage of patients with severe or substantial headache impact (HIT-6 score ≥56) at each time point b.



Lipton RB, et al. *Cephalalgia* 2016;36(9):899-908.

Admission Criteria: Non-emergent

- Failed outpatient treatment including 3 days in infusion center (and significant disability or medication overuse) – OR
- Significant psychiatric comorbidity – OR
- Significant medical comorbidity (infusion not safe or appropriate) – OR
- Daily opioids or barbiturates

DISABILITY

AHS Expert Panel Guidelines for ED Management (Appropriate for Infusion Centers)

- Identified 68 unique RCTs utilizing 28 injectable medications.
  - 19 were rated class I (low risk of bias), 21 were rated class II (higher risk of bias), and 28 were rated class III (highest risk of bias)
- Level B: metoclopramide, prochlorperazine, and sumatriptan each had multiple class I studies supporting acute efficacy, as did dexamethasone for prevention of headache recurrence
- All other medications had lower levels of evidence
- Recommendations could not be made for parenteral dexamethasone, injectable versions of DHE, ergotamine, ketamine, and lysine clonixinate; and IV formulations of magnesium, meperidine, and nalbuphine

Orr SL, et al. *Headache*. 2016;56(7):911-940.

Inpatient Management of Migraine

Dihydroergotamine (DHE):

- DHE is mainstay for treatment of refractory CM patients
- Nausea affects 58% of patients and results in cessation of DHE infusion in 4%, predicts worse outcomes[1]
- Infusion related headache is NOT a predictor of worse outcomes
- Domperidone[2] and aprepitant, a substance P antagonist/ neurokinin 1 receptor[3]

IV Ketamine*:

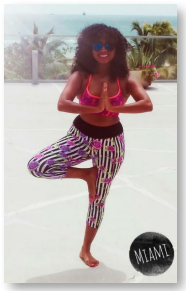
- Phencyclidine derivative antagonist of NMDA receptors, helpful in refractory CM according to retrospective study, n = 77[4]
- Mean headache pain rating (0-10 pain scale) was an average of 7.1 at admission and 3.8 on discharge ($P < .0001$)[4]
- The majority (55/77, 71.4%) of patients were classified as acute responders defined as at least 2-point improvement in headache pain at discharge[4]
- Some (15/77, 27.3%) acute responders maintained this benefit at their follow-up office visit but sustained response did not achieve statistical significance.[4]

*Not FDA approved for chronic migraine

1. Nagy AJ, et al. *Neurology.* 2011;77(20):1827-1832.; 2. Robbins NM, et al. *Neurology.* 2016;87(24):2522-2526.;
3. Chou DE, et al. *Neurology*. 2016;87(15):1613-1616.; 4. Pomeroy JL, et al. *Headache*. 2017;57(2):276-282.

Behavioral Interventions

- The yoga reduces migraine frequency[1] and severity[2]
- Yoga promotes reduced vagal tone and decreased the sympathetic drive[3] vascular markers[4]
- Mindfulness-based Stress Reduction (MBSR) improves pain and quality of life[5]
- In 2007 meta-analysis, the frequency of migraine attacks and perceived self-efficacy demonstrated the strongest improvements[6]
- In a pediatric chronic migraine study, CBT and amitriptyline was superior to education plus amitriptyline to reach the clinically meaningful outcome of ≤4 headache days/month[7]



[1]John PJ, et al. *Headache*. 2007;47(5):654-66; [2]Boroujeni MZ, et al. *Adv Biomed Res*. 2015;4:259; [3]Kisan R, et al. *Int J Yoga*. 2014;7(2):126-132; [5]Bakhshani NM, et al. *Glob J Health Sci*. 2015;8(4):142-151; [6]Nestoriuc Y, et al. *Pain*. 2007;128(1-2):111-127.; [7]Kroner JW, et al. *Headache* 2016;56(4):711-6.

Complementary Options

AAN Guidelines for Migraine Prevention 2010

- Petasites (butterbur) 50-75 mg bid (level A)- emerging safety concerns***
- Magnesium 600 mg (level B)
- Riboflavin 400 mg/day (level B)
- Feverfew 50-300 mg bid (level B)
- Coenzyme Q10 100 mg tid (level C)

Additional Options:

- Ginger 250 mg - RCT showed efficacy comparable to vs sumatriptan (n = 100)
- Melatonin 3 mg- RCT showed efficacy comparable to amitriptyline without side effects
- Vitamin D for patients taking simvastatin?
- Acupuncture
- Lavender (aromatherapy)

Loder E, et al. *Headache*. 2012;52(6):930-945

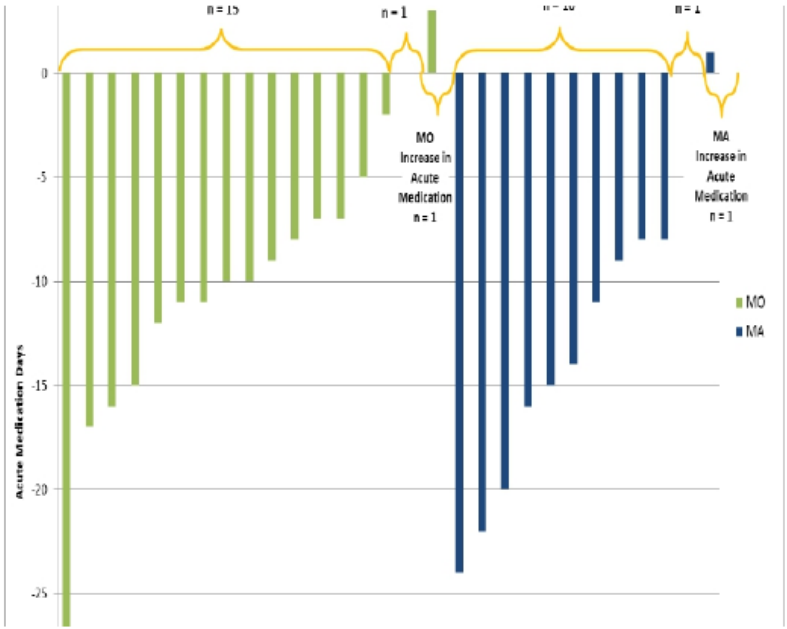
Non-Invasive Nerve Stimulation

Mechanism	Device	Clinical phase
Acute treatment		
Transcutaneous magnetic stimulation (TMS)	Cerena/Spring TMS	Phase II (published)
Vagal nerve stimulation	GammaCore	Open-label, pilot study
Sphenopalatine ganglion stimulation	ATI device	Ongoing CM study
Occipital Nerve Stimulator	Medtronics Boston Scientific Precision System	Open label, ONSTIM trial OPTIMISE trial
Preventive treatment		
Supraorbital/supratrochlear nerve stimulation	Cefaly	Phase II (FDA approved)
Vagal nerve stimulation	GammaCore	Small RCT for chronic migraine
Repetitive TMS	Spring TMS	Ongoing study

Miller S, et al. *Pract Neurol*. 2016 May 5. [Epub ahead of print]

sTMS Open Label Study: Pulsed BID and PRN

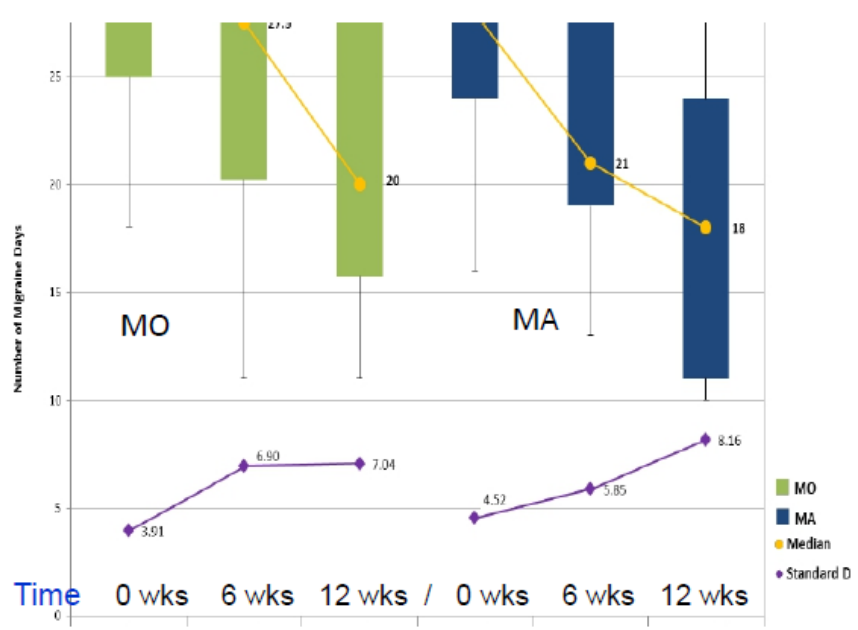
Reduction Acute Medicine Days



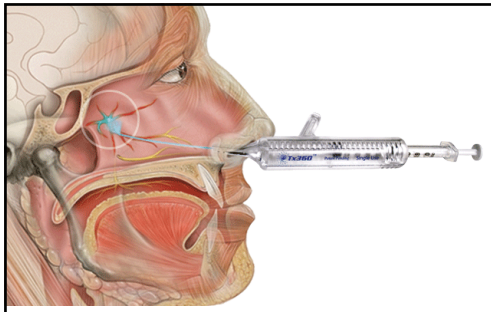
Migraine wo aura
N = 29

Migraine w/aura

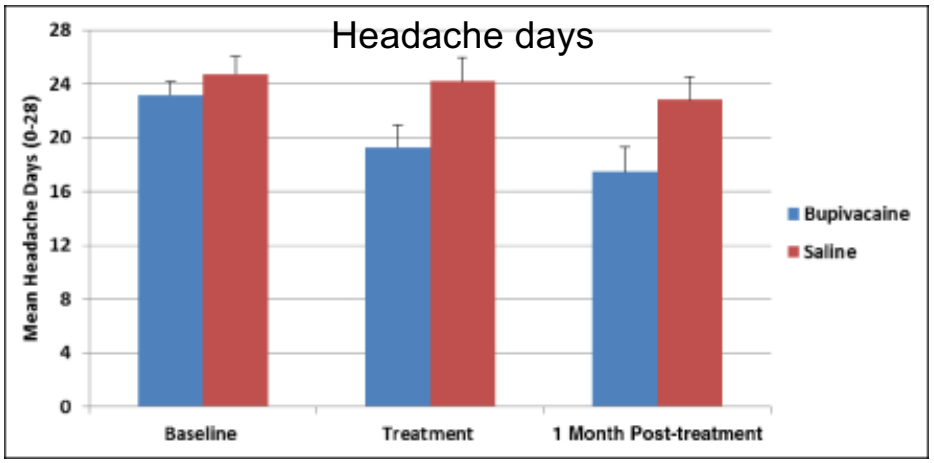
Reduction Migraine Days



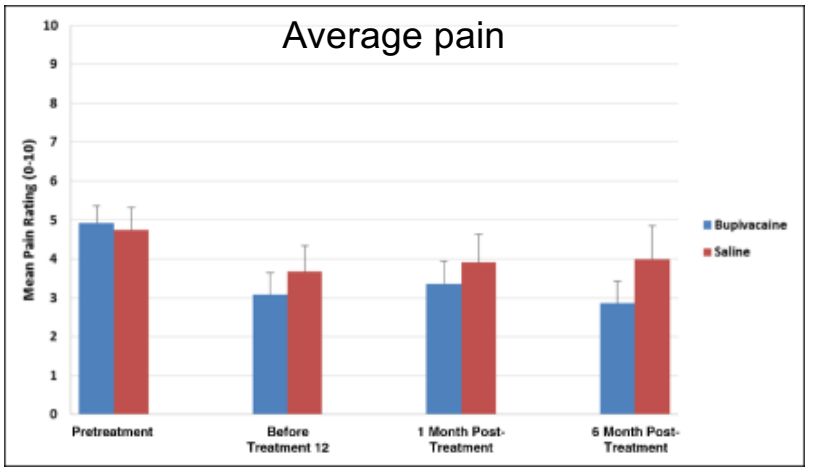
Bhola R, et al. Presented at AHS Scientific Meeting, June 2015.



A Double-Blind, Placebo-Controlled Study of Repetitive Transnasal Sphenopalatine Ganglion Blockade With Tx360® as Acute Treatment for Chronic Migraine



The number of headache days were consistently lower at the end of treatment and 1 month post-treatment for the bupivacaine group compared to the saline group.

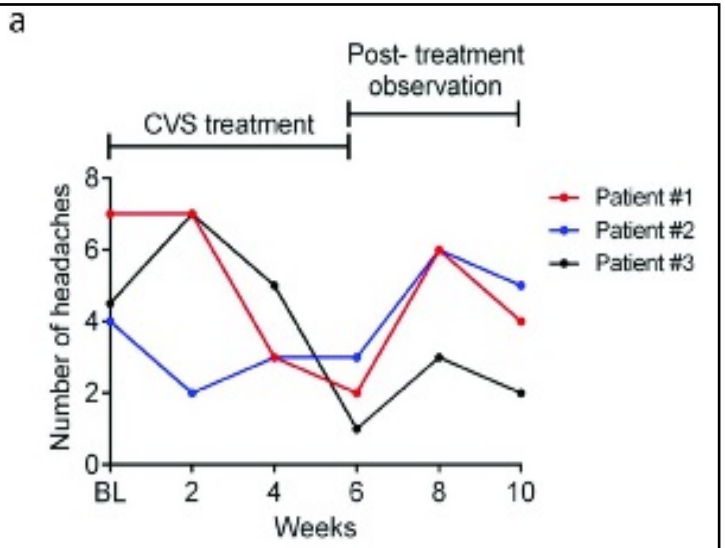


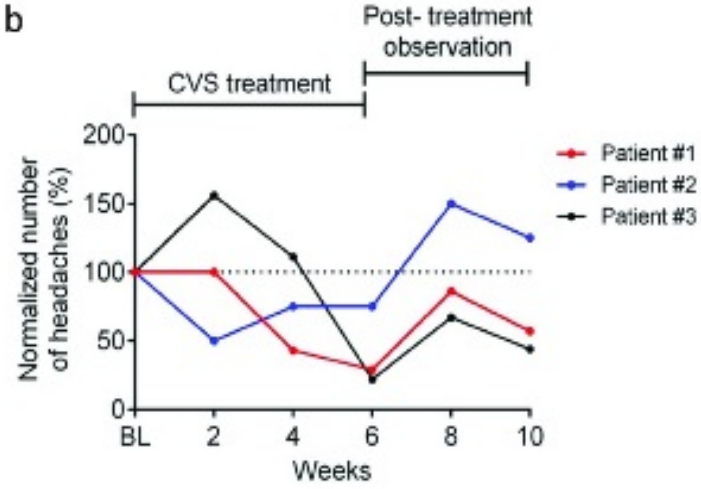
Protocol: 2/week for 6 weeks. Average pain last 24 hours. Average pain scores were lower for the bupivacaine group compared with the saline group at treatment 12, 1 month post-treatment, and 6 months post-treatment.

Headache: The Journal of Head and Face Pain. 2015;55(4):529-542.
http://onlinelibrary.wiley.com/doi/10.1111/head.12546/full#head12546-fig-0003

Caloric Vestibular Stimulation (CVS)

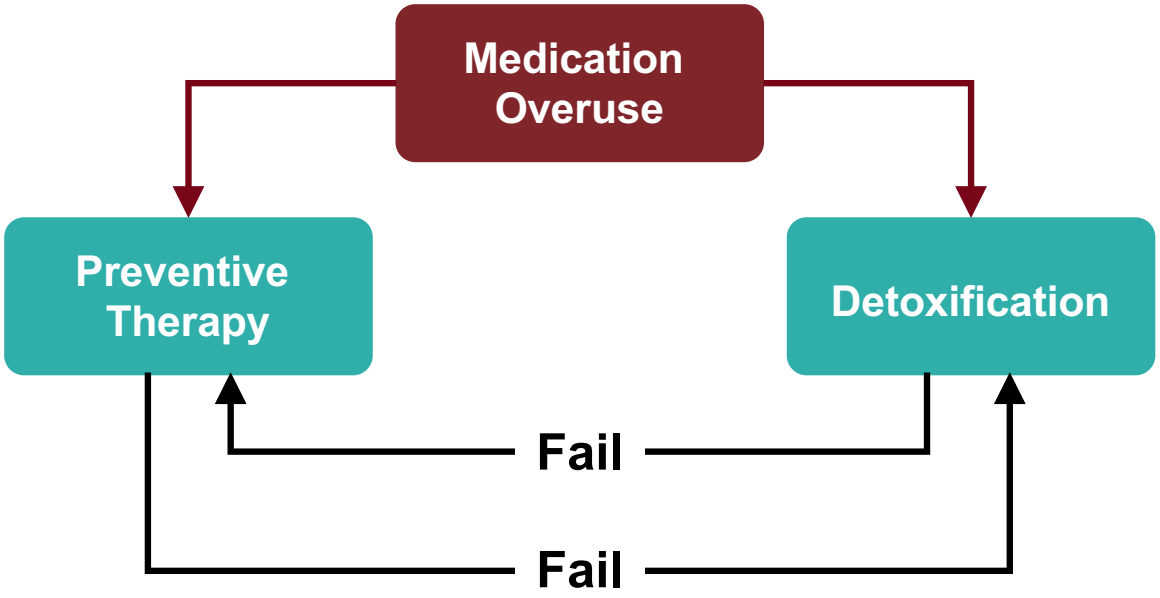
- Delivers tightly controlled time-varying thermal waveforms, programmed through an external control unit.
- Several safety features, which limit patients to the prescribed waveform (preventing the potential for temperature extremes).
- CVS treatment with time-varying elicits changes in cerebral blood flow physiology consistent with the neuromodulation of brainstem centers.
- Safely and feasibly shown to treat episodic migraine.





Black RD, et al. *IEEE J Transl Eng Health Med.* 2016;4:2000310.

Optimal Strategy for Treating Medication Overuse Headache?



Bigal RB, Lipton RB. *Neurology*. 2008;71(22);1821-8.
Diener HC, Limmroth V. *Lancet Neurol*. 2004;3(8):475-483.
Hagen K, et al. *Cephalalgia*. 2009;29(2):221-232.

Lasmiditan: 5-HT1F Receptor Agonist

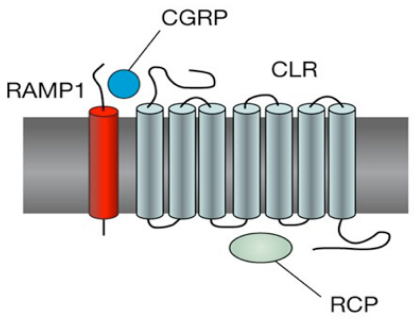
- Phase 2b study results: the 2-h headache response rates at four studied doses of lasmiditan (LAS) ranged from 34 to 52 %, all of which were superior to the 21 % 2-h response rate in the placebo group (p B .025).
- These studies have shown no evidence of drug-related cardiovascular adverse effects or chest symptoms, and the drug does not seem to constrict blood vessels.

Rizzoli PB, *Neuropsychiatr Dis Treat*. 2014;10:547-552.

- Some patients have developed dose-dependent side effects such as paresthesia, dizziness, fatigue, and nausea.
- Notably, dizziness was experienced by 26% of subjects receiving the 100 mg dose vs. 0% of patients receiving placebo [6].
- A phase 3 trial studying LAS for acute migraine treatment is planned. Study will include patients with CV risk factors, which is significant given that cardiovascular disease is listed as a contraindication in the manufacturer's package inserts for all 7 available triptans.

Calcitonin Gene-Related Peptide (CRGP)

- Formed by alternative splicing of the calcitonin gene
- Released in the jugular venous system in response to the activation of the trigeminovascular system , severe attacks, and interictally (chronic>episodic)
- Located in sensory nerve endings of cranial blood vessels
- Potent dilator of cerebral arteries
- Found in central trigeminal system and many brain regions
- Ideal for those with triptan contraindications (non-vasoconstrictive)

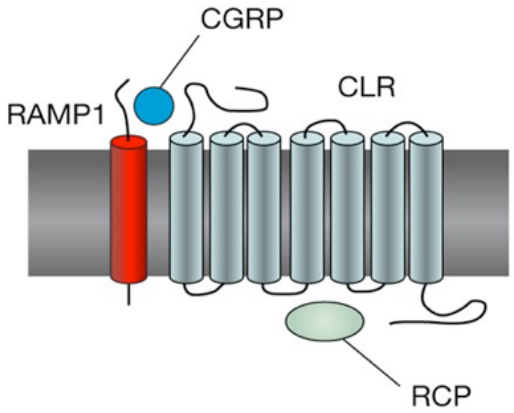


CGRP receptor in migraine

Wrobel Goldberg S, et al. *CNS Drugs*. 2015;29(6):443-452.

CGRP Targets and Migraine: The Rationale

- CGRP levels are normalized by sumatriptan
- CGRP is persistently elevated in chron migraine
- CGRP blockade in the TNC, thalamus effective in blocking the trigeminonociception in animal models
- Small molecule receptor antagonist effective treatments for acute migraine (BMS-927711, BI44370TA, MK-1602 etc)



CGRP receptor in migraine

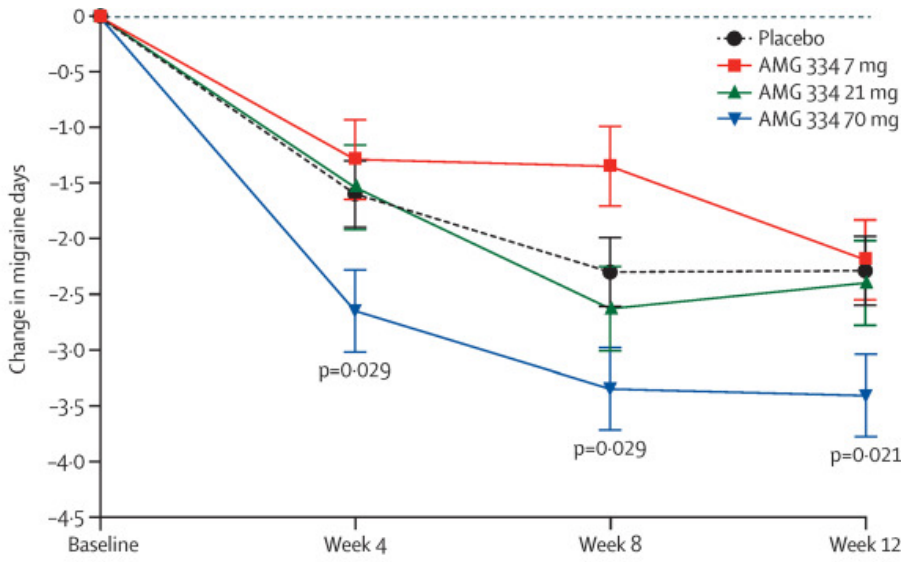
Cauchi M, et al. *J Neurol*. 2016;263(1):192-194.

Monoclonal Antibodies Against CGRP Pathway

Target	AMG 334 CGRP Receptor	LY2951742 CGRP Ligand	TEV-48125 CGRP Ligand	ALD403 CGRP ligand
Route of Administration	SC	SC	SC	IV
T 1/2	Not disclosed	25-35 days	Around 45 days	Around 32 days
Frequency	Monthly	Every 2 weeks (2a) and monthly (2b)	Monthly	Every 3 months IV and monthly for SC
Migraine Prophylaxis Indication	Episodic and chronic	Episodic and chronic	Episodic and chronic	Episodic and chronic
Status	Episodic Phase IIb complete	Episodic Phase IIb complete	Phase IIb complete (chronic and episodic)	Episodic Phase IIb complete
Safety	Safe and tolerated	Safe and tolerated	Safe and tolerated	Safe and tolerated

Fiala JL, et al. *Nat Rev Drug Discov*. 2016;15(1):8-9.

Safety and Efficacy of AMG 334 for Prevention of Episodic Migraine: Randomized, Double-Blind, PBO-Controlled, Phase 2 Trial

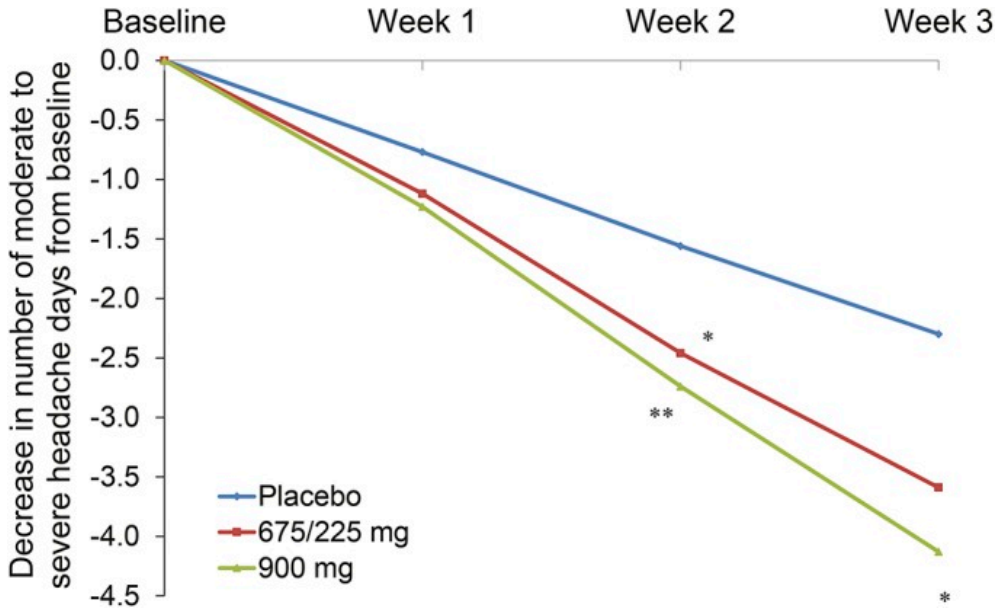


Number of patients				
Placebo	153	151	144	144
AMG 334 7 mg	107	107	106	104
AMG 334 21 mg	102	99	97	93
AMG 334 70 mg	104	103	103	99

- Mean change in monthly migraine days at wk 12 was −3·4 (SE 0·4) days with AMG 334 70 mg vs. −2·3 (0·3) days with PBO (difference −1·1 days [95% CI −2·1 to −0·2], *p* = ·021)
- Adverse events were recorded in 82 (54%) patients who received PBO, 54 (50%) patients in AMG 334 7 mg group.

Change from baseline in mean monthly migraine days Data are least squares means. *p* value is for PBO vs. 70 mg group.
Sun H, et al. *Lancet Neurol.* 2016;15(4):382-390.

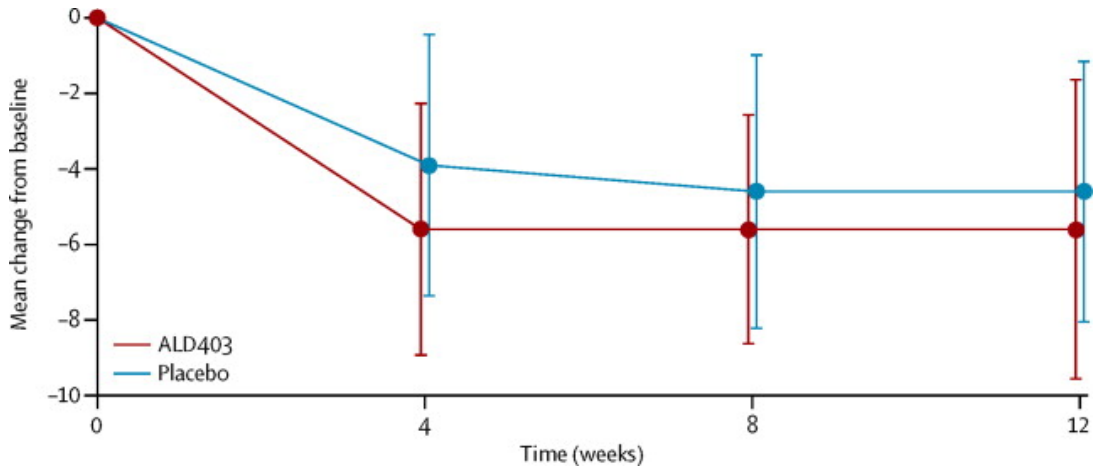
TEV-48125 for the Preventive Treatment of Chronic Migraine



Change from baseline in the number of headache days of at least moderate severity
*p < .05, **p < .01.
Bigal ME, et al. *Neurology* 2016;87(1):41-48.

- TEV-48125 significantly decreases the number of headache hrs within 3-7 days of injection.
- For both 675/225-mg and 900-mg doses, the improvement was sustained through the 2nd (p = .004 and p < .001) and 3rd (p = .025 and p < .001) wks of therapy and throughout the study (mon 3, p = .0386 and p = .0057).
- For change in weekly headache days of at least moderate intensity, both doses were superior to PBO at wk 2 (p = .031 and p = .005).

Safety and Efficacy of ALD403, an Antibody to CGRP for the Prevention of Frequent Episodic Migraine

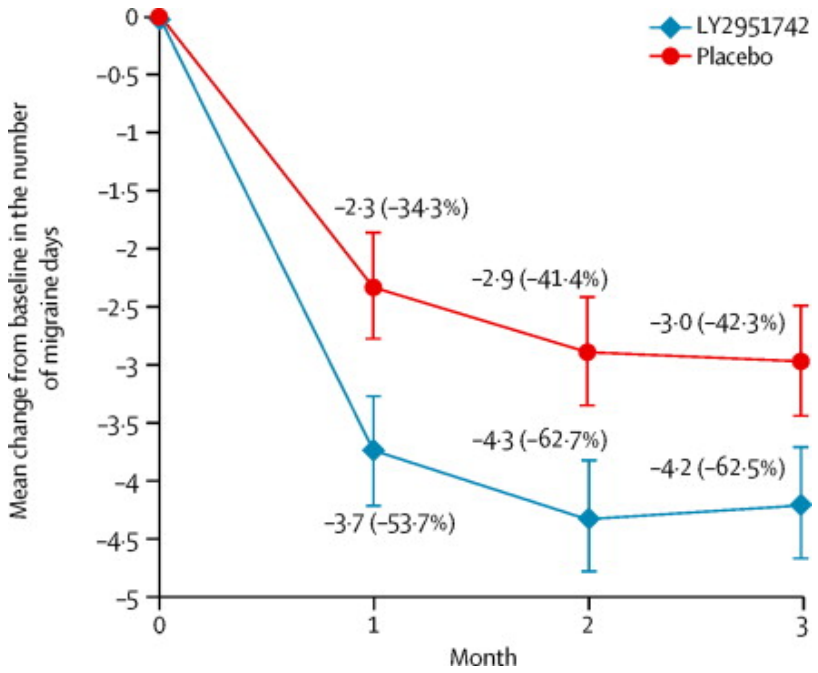


Change in migraine days per month compared with baseline
Bars are SD

- Mean change in migraine days between baseline and wks 5–8 was −5·6 (SD 3·0) for the ALD403 group vs. with −4·6 (3·6) for the PBO group (difference −1·0, 95% CI −2·0 to 0·1; one-sided p = 0·0306).
- Adverse events were experienced by 46 (57%) of 81 patients in the ALD403 group and 43 (52%) of 82 in the PBO group.
- Serious side effects unrelated to the study.

Dodick DW, et al. *Lancet Neurol*. 2014;13(11):1100-1107.

Safety and Efficacy of LY2951742, a Monoclonal Antibody to CGRP, for the Prevention of Migraine: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study



Mean change from baseline in the number of migraine headache days during the treatment period. Bars show the 90% CIs. *p* values were not calculated for months 1 and 2.

Dodick DW, et al. *Lancet Neurol*. 2014;13(11):1100-1107

- Mean change from baseline to week 12 in the number of migraine headache days was −4·2 (SD 3·1; 62·5% decrease) in the LY2951742 group compared with −3·0 (SD 3·0; 42·3% decrease) in the placebo group (least-squares mean difference −1·2, 90% CI −1·9 to −0·6; *p* = .0030).
- Adverse events that occurred more frequently with LY2951742 than with PBO included injection site pain, erythema, abdominal pain.
- 2 serious adverse events were unrelated.

Conclusions

- Migraine remains underdiagnosed and undertreated and has high levels of disability. Appropriate evidenced based treatments exists to improve the quality of life.
- There are a number effective non-pharmacological and pharmacological therapies or technologies as part of an individualized multimodal migraine management plan.
- Discussions about the psychosocial impact, comorbidities and disability may improve personalized care.
- The latest evidence-based research on emerging therapies for migraine remains promising.

Questions & Answers

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