



Episodic Versus Chronic Migraine: An Update on Novel & Emerging Therapeutic Options

Theresa Mallick-Searle, NP

Disclosure

- *Consultant/Independent Contractor:* Novartis
- *Honoraria:* Amgen, Lilly



Learning Objectives

1. Define episodic and chronic migraine
2. Discuss new formulations within existing drug classes
3. Explore novel/emerging therapies for migraine treatment



Migraine


One of the Top 10 Causes of Years Lived With Disability Worldwide

Prevalence:

- Women 25% (lifetime)
- Men 8% (lifetime)
- >30 million Americans have migraines (12% of the population)
- Highest from 25-50 years of age

Categories:

- With or w/o aura
- Episodic (0-14 headache days/month)
- Chronic (15+ headache days/month)



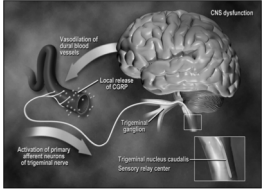
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Pathophysiology (neurovascular theory)

Neurogenic inflammation eventually leads to the pain associated with a migraine.

Complex neuro-vascular contributing factors:

- Cortical spreading depression.
- Reduction in brain electrical activity & decrease in blood flow.
- Release of K⁺ and H⁺ activates sensory fibers.
- Activation of trigeminal & brain stem neurons.
- Precipitation of vasodilation.



Migraine is progressive during an attack → Central sensitization.

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Transformation

2.5% annually → episodic migraine → chronic migraine

Factors associated with an ↑ risk of transformation:

obesity – snoring - sleep disorders - excessive caffeine intake - psychiatric disease
 high frequency of headaches at baseline - frequent use of abortive migraine drugs
 female - lower socioeconomic status - comorbid pain disorders - history of head or neck injury - presence of cutaneous allodynia

Major life changes: divorce – marriage - employment status

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Migraine Is Under-Recognized & Undertreated

26.3% Episodic migraine patients	4.5% Chronic migraine patients
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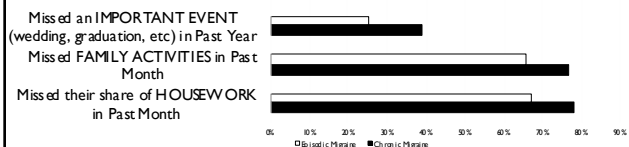
Consulted a healthcare professional, received an accurate diagnosis, and were prescribed appropriate treatment.

Based on the AMPP (n=775) & CaMEO (n=1,254) studies



Burden of Disease: Chronic migraine epidemiology and outcomes study (CaMEO)

Impact of migraine on patients' FAMILY & SOCIAL LIVES Based on the CaMEO study (n=4,022)



Burden of Disease: American Migraine Prevalence & Prevention Study (AMPP)

Work Productivity
30% reported that their productivity at work was ↓ by at least 50% in the previous 3 months .

Home Productivity
>75% reported that household productivity was ↓ by at least 50% in the previous 3 months.

Missed leisure time & activities
45% of people reported missing family, social, and leisure activities .



Migraine: Diagnostic Criteria ICHD-3

At Least 5 Episodes/lifetime Fulfilling the Criteria Below

☑ Headache lasting 4-72 hours

AND

✓

AND

✓

EPISODIC MIGRAINE (EM)

<15 Headache Days a month

↔

CHRONIC MIGRAINE (CM)

15+ Headaches Days a month


Therapies

Pharmacological

- > migraine specific
- > migraine non-specific
- > acute treatment
- > preventative treatment

Non-pharmacological

- > behavioral/lifestyle
- > intervention
- > complementary



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<u>Non-specific Treatments</u>	<u>Specific Treatments</u>
<p>Reduce pain through general pain pathways</p> <ul style="list-style-type: none"> > OTC analgesics > Antiepileptics > Antidepressants > Anti-emetics (dopamine receptor antagonists) > Opioids/barbiturates > Muscle relaxants 	<p>Reduce pain through direct actions trigeminovascular system including 5HT1B/D/F receptors</p> <ul style="list-style-type: none"> > Triptans > Dihydroergotamine (DHE) > Ergotamines > CGRP antagonists <p style="text-align: center; font-size: small;">Calcitonin gene related peptide (CGRP)</p>

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Acute Treatments

Basic Principals:

- Patient preference
- Side effects/safety/efficacy
- Education about use
- Goals of care

Sustained freedom from pain with no adverse events (SNAE):

- Freedom from pain within 2 hours.
- Return to normal function/activities.
- No use of rescue medicine/headache recurrence within 24 hours.
- Patient satisfaction.
- No adverse events.

(Dodick DW, et al. 2007)



LEVEL A	LEVEL B	LEVEL C	LEVEL U	OTHER
Analgesics Acetaminophen 1000 mg	Antiemetics <ul style="list-style-type: none"> ▪ Chlorpromazine IV 12.5 mg ▪ Droperidol IV 2.75 mg ▪ Metoclopramide IV 10 mg ▪ Prochlorperazine IV/IM 10 mg, PR 25 mg 	Antiepileptics Valproate IV 400-1000 mg	NSAIDs Celecoxib 400 mg	Octreotide SC 1000 mcg
Ergots DHE: <ul style="list-style-type: none"> ▪ nasal spray 2 mg ▪ pulmonary inhaler 1 mg 	Ergots <ul style="list-style-type: none"> ▪ DHE: IV/IM/SC 1 mg ▪ Ergotamine/caffeine 1/100 mg 	Ergots Ergotamine 1-2 mg	<ul style="list-style-type: none"> ▪ Lidocaine IV ▪ Hydrocortisone IV 50 mg 	<ul style="list-style-type: none"> ▪ Chlorpromazine IM 1mg/kg ▪ Granisetron IV 40-80 mcg/kg
NSAIDs <ul style="list-style-type: none"> ▪ ASA 500 mg ▪ Diclofenac 50, 100 mg ▪ Ibuprofen 200, 400 mg ▪ Naproxen 500, 550 mg 	NSAIDs <ul style="list-style-type: none"> ▪ Flurbiprofen 100 mg ▪ Ketoprofen 100 mg ▪ Ketorolac IV/IM 30-60 mg 	NSAIDs Phenazone 1000 mg (Marmura MJ, et al. 2015)		Ketorolac - tromethamine nasal spray

LEVEL A	LEVEL B	LEVEL C	LEVEL U	OTHER
Opioids Butorphanol nasal spray 1 mg		Opioids <ul style="list-style-type: none"> ▪ Butorphanol IM 2 mg ▪ Codeine 30 mg oral ▪ Meperidine IM 75 mg ▪ Methadone IM 10 mg ▪ Tramadol IV 100 mg 		Acetaminophen IV 1000 mg
Triptans (see table below)	<ul style="list-style-type: none"> ▪ MgSO4 IV (migraine w/aura) 1-2 gram ▪ Isometheptene 65 mg 	Dexamethasone IV 4-16 mg		
Combinations <ul style="list-style-type: none"> ▪ Acetaminophen/aspirin/caffeine 500/500/130 mg ▪ Sumatriptan/naproxen 85/500 mg 	Combinations <ul style="list-style-type: none"> ▪ Codeine/acetaminophen 25/400 mg ▪ Tramadol/acetaminophen 75/650 mg 	<ul style="list-style-type: none"> ▪ Butalbital 50 mg ▪ Lidocaine intranasal ▪ Butalbital/acetaminophen/caffeine/codeine 50/325/40/30 mg ▪ Butalbital/acetaminophen/caffeine 50/325/40 mg 		(Marmura MJ, et al. 2015)

Triptans	Formulations	Doses	Max daily	Notes
sumatriptan (Imitrex)	Tablets Nasal spray Intra-nasal powder SC injections Suppositories	25, 50, 100 mg 5, 20 mg 11 mg 4, 6 mg 25 mg	200 mg 40 mg 44 mg 12 mg 50 mg	Off-label ages 6+ SC 3-6 mg max 12 mg/24h & ages 5+ Nasal spray max 40 mg/24h Try 100 mg dose first, reduce if side effects. SC 6 mg for cluster headaches.
zolmitriptan (Zomig)	Tablets Oral dissolving Nasal spray	2.5, 5 mg 2.5, 5 mg 2.5, 5 mg	10 mg 10 mg 10 mg	FDA labeled ages 12+ Nasal spray max 10 mg/24h
rizatriptan (Maxalt)	Tablets Oral dissolving	5, 10 mg 5, 10 mg	30 mg 30 mg	FDA labeled ages 6-17 (5-10 mg) Lower dose if using propranolol as prophylaxis.
naratriptan (Amerge)	Tablets	1, 2.5 mg	5 mg	Only triptan NOT contraindicated with MAOI, slower onset. Low SE profile.
almotriptan (Axert)	Tablets	12.5 mg	25 mg	FDA labeled ages 12-17 (6.25, 12.5 mg)
frovatriptan (Frova)	Tablets	12.5 mg	25 mg	Longest half-life: 25 hr, slow onset
eletriptan (Relpax)	Tablets	20, 40 mg	80 mg	Try 80 mg first, reduce if side effects.

Emerging therapy – acute treatment

Name	Molecular Format	Target	Status	Indications
lasmiditan	Oral, selective serotonin 5-HT1F receptor agonist	5-HT1F	FDA Review	Acute treatment
ubrogepant	Small molecule CGRP antagonist	CGRP	FDA Acceptance	Acute treatment
rimegepant	Small molecule CGRP antagonist	CGRP	FDA Review	Acute treatment

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Role of the CGRP polypeptide in acute migraine

Basic Principles:

- CGRP administration triggers migraine.
- CGRP is released during a migraine attack.
- CGRP levels are elevated in chronic migraine.
- Small molecule CGRP antagonists (gepants) abort migraine.
- Antibodies to CGRP/or its receptor prevent migraine.
- Lack of vasoconstriction/vascular side effects
- Efficacy comparable to triptans

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Preventative Treatments

Consider preventative therapy when:

- ≥4 Migraine headache days/month
- Attacks lasting for several days per week
- Severity/frequency that critically impacts daily life
- Abortive therapies are contraindicated, ineffective, overused, not tolerated
- Uncommon migraine type (hemiplegic, basilar, prolonged aura)



Preventative Treatments

- Antidepressants
 - Antiepileptics
 - Antihypertensives
 - Calcitonin-gene-related-peptides (CGRPs)
 - Monoclonal antibodies (mAB)
 - Neutraceuticals
 - OnabotulinumtoxinA (Botox™)
- Educate headache sufferers about their condition & treatment options, trigger identification (avoidance).
- Educate about medication overuse headache.



Antiepileptics	Beta-blockers	Triptans	Other
Divalproex sodium 250-500 mg BID (level A)	Metoprolol 25-100 mg BID (level A)	Frovatriptan (menstrual migraine prophylaxis) 2.5 mg qd-BID x6 days, starting 2 days prior to menses	Onabotulinumtoxin A (PREEMPT paradigm q12 weeks)
Valproic acid 250-500 mg BID (level A)	Propranolol 160-240 mg/daily (level A) * Start at 80 mg		Petasites (butterbur) Level A in 2012; NO LONGER RECOMMENDED.
Topiramate 50-100 mg BID (level A)	Timolol 10-30 mg/daily (level A)		(Silberstein, et al. 2012)

Antidepressants	Beta-blocks	Triptans	Other
Amitriptyline (level B) 10-100 mg daily	Atenolol 50-150 mg daily (level B) * Start at 25 mg	Naratriptan (menstrual migraine prophylaxis) 1 mg BID x5 days, starting 2 days prior to menses	Supplements (see below)
Venlafaxine (level B) 150 mg ER daily	Nadolol 80-160 mg daily (level B) * Start at 40 mg	Zolmitriptan (menstrual migraine prophylaxis) 2.5 mg bid-tid x7 days, starting 2 days prior to menses	(Silberstein, et al. 2012)

Angiotensin receptor blockers (ARBs)	Calcium Channel Blockers
Candesartan 4-32 mg daily (level C)	Verapamil 160-240 mg (level U) * Start at 60 mg
Ace Inhibitors	Antiepileptics
Lisinopril 10-40 mg daily (level C)	Carbamazepine (FDA trigeminal neuralgia) 200-400 mg BID

(Silberstein, et al. 2012)

Calcitonin Gene Related Peptide – antagonists (CGRPs)

Monoclonal antibodies targeting the CGRP receptor

- erenumab - 70-140 mg sc monthly injection.

Monoclonal antibodies targeting the CGRP molecule

- galcanezumab - 240 mg loading dose, 120 mg sc monthly injection.
- fremanezumab - 225 mg sc monthly injection/ alt 675 mg sc q3 months.

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Calcitonin Gene Related Peptide – antagonists (CGRPs)

- Current theory of migraine pathology → activation of trigeminal ganglion nociceptive neurons → release of CGRP (not substance P or neurokinin A) → implicated in migraine pathology.
- CGRP is widely distributed in the central & peripheral nervous system, expressed in C & Aδ nerve fibers → transmit nociceptive signals to the central nervous system (CNS).



Calcitonin Gene Related Peptide – antagonists (CGRPs)

Although a complete understanding of the pathogenesis of migraine is not clear, several lines of evidence in migraineurs support a role of CGRP as a key mediator of migraine pathology.

- CGRP levels in the cranial circulation & saliva are ↑ during a migraine attack.
- Successful treatment of migraine pain with triptan drugs, resulted in the normalization of CGRP levels.
- Infusion of human CGRP could provoke a migraine attack in susceptible individuals.



**Indications for initiating treatment with mAbs
CGRP antagonists: AHS Consensus 2019**

- Episodic Migraine (both apply)
- > Failed treatment related to side effects or inadequate response after 6 weeks of at least two Level A/B preventative therapies (AAN-AHS).
 - > At least moderate disability (MIDAS >11, HIT-6 >50)
- Chronic Migraine (either apply)
- > Failed treatment related to side effects or inadequate response after 6 weeks of at least two Level A/B preventative therapies (AAN-AHS).
 - > Failure minimum 2 quarterly injections (6 months) onabotulinumtoxinA.

AHS Consensus Statement

The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice



Emerging therapy – preventative treatment

<u>Name</u>	<u>Molecular Format</u>	<u>Target</u>	<u>Status</u>	<u>Indications</u>
eptinezumab	Humanized IgG ₁	CGRP	FDA Review	Migraine prevention
atogepant	Small molecule CGRP antagonist	CGRP	Phase 2b/3	Episodic migraine prevention



Onabotulinumtoxin A

- FDA approved for chronic migraine prevention
- Administered every 12 weeks
- Studied protocol: 31 injection sites into 7 muscle groups
- Requires training upfront



• Botulinum toxin injection sites for treating chronic migraines



Interventions

- Occipital nerve blocks
- Sympathetic nerve blocks (stellate ganglion)
- Supraorbital & infraorbital nb
- Cervical epidural
- Supratrochlear nb
- Cervical medial branch blocks
- Auriculotemporal nb
- Intranasal (sphenocath, Tx360)
- Trigger point injections



Neuromodulation – Invasive

Neurostimulation is FDA-approved for the treatment of certain intractable pain syndromes, although it is not approved for headache, chronic migraine, and craniofacial pain.

- Occipital Nerve Stimulator
- Supraorbital nerve stimulation
- Infraorbital nerve stimulation

- Subcutaneous electrical conduction
- Dermatome stimulation
- Myotomal stimulation
- Sympathetic stimulation
- Local blood flow alteration
- Peripheral nerve stimulation
- Peripheral and central neurochemical mechanisms
- Trigeminovascular system & Trigemino-cervical tract



Neuromodulation – Invasive



Sphenopalatine ganglion (SPG) stimulator - <http://www.ati-spg.com/us/en/>

- SPG stimulation has been an available therapy for episodic and cluster headache in Europe since 2012.
- US trials for cluster headache on going.

The ATI™ Neurostimulation System delivers low-level energy directly to the area of the SPG.

- A miniaturized neurostimulator with an integral lead.
- The Remote Controller: A hand-held device with on-demand patient-controlled SPG stimulation therapy.



Neuromodulation – None Invasive

sTMS mini™

- Acute and preventative treatment of migraine headache in Individuals 12+.
- Stimulates the occipital cortex.



<http://www.eneura.com/#>

Contraindicated:

- Metal in the head, neck, or upper body that is attracted by a magnet.
- Implanted medical device (e.g., pacemaker, deep brain stimulator).
- epilepsy or who have a personal or family history of seizures.

<http://www.eneura.com/prescribing-resources/>



Neuromodulation – None Invasive

Cefaly™

- First FDA-approved external trigeminal nerve stimulation device.
- ACUTE - PREVENT - DUAL



<https://www.cefaly.us/en/questions>

<https://www.cefaly.us/en/migraine-treatment-cefaly>



GammaCore™

- Vagus nerve stimulator (nVS) for the treatment of migraine pain in adults.
- ACUTE – PREVENTION
- Cluster Headache indication

<https://www.gammacore.com/prescribing-gammacore/>

<https://www.gammacore.com/>



Nervio Migra: <https://theranica.com/>

Attached to the patient's arm (below the shoulder), is controlled by intuitive smartphone applications - acute migraine treatment FDA approved.

Real-time Efficiency Control

- Maximum Effectiveness (ME) mechanism. ME collects and evaluates measurements of EMG (Electromyography) signals from the treated muscle, as a response to the stimulation.
- This information is processed in our chip, providing guidelines to how optimally adjust the location of the electrodes and/or the level of the stimulation intensity in order to maximize muscle stimulation efficiency.





How it works



Fully-integrated and self-contained: Nervio patches contain ENS/NMES electrodes, a battery, and our proprietary-developed smart chip.



Use a smartphone or tablet to download and install our pain management app.



We use BLE wireless communication. Launching the App pairs the mobile device with Theranica's patches.



The electrical pulses, generated by the chip, stimulate the sensory nerves under the skin, resulting in pain relief.

Complementary

- Acupuncture
 - Aroma Therapy
 - Essential Oils
 - Cognitive behavioral therapy (CBT)
 - Progressive muscle relaxation
 - Mindfulness/stress reduction
 - Biofeedback
 - Nutraceuticals
- In a recent systematic review, CBT showed a ↓ in headache intensity by 16.2%-71.9%, ↓ of medication intake by 20%-25%, ↓ depression, anxiety & pain catastrophizing while ↑ pain acceptance & coping (Raggi, 2018).
- A meta-analysis of 22 trials showed that acupuncture leads to a 50% ↓ in headache frequency in 41-57% of the patients compared with (no acupuncture, sham or prophylactic medication therapy).
- Suggesting that acupuncture is slightly more effective than sham and as effective as medication prophylaxis (Xu, 2018).



Nutraceuticals/supplements/micronutrients

- Level A**
Butter (parasites) 50-100 mg BID
- Level B**
- Magnesium (Mg) 200-400 mg BID
 - Riboflavin (Vit-B2) 400mg daily
 - Feverfew (MIG-99) 100-300 mg daily
- Level C**
CoQ10 100 mg TID
- For women of childbearing age, avoid CoQ10.
- Most micronutrients safe in children, but clinical studies are few.
- Avoid feverfew & CoQ10 for patients on antidepressants.
- Avoid Mg, MIG-99, CoQ10 for patients on anticoagulation.



Summary

- mAb targeting CGRP are at the forefront of current treatment (acute and preventative) for episodic and chronic migraine.
- Peripheral nerve blocks (PNB) widely used in headache (and pain) practices.
- 69% of American Headache Society members reported having had PNBs (Blumenfeld, 2010).
- 45-88% patients report improvement with PNBs (Tobin, 2009).
- Anatomical targets for neuromodulation range from central to peripheral, largely MOA is through inhibitory pathways (gate-control).
- The currently available devices have shown efficacy in prevention and acute treatment (studied mostly in migraine and cluster headaches).
- Approximately 50% of >30 million Americans with migraine have reportedly tried complementary therapies (Burch, 2015; Wells, 2011).

Resources

Migraine Apps (tracking and self-help):

- iHeadache (iPhone)
- Migraine Buddy (iPhone)
- Migraine Diary (Android)

Relaxation Apps:

- Relax Melodies (iPhone & Android)
- Sleep Time (iPhone & Android)
- What's up? (iPhone & Android)

Online tools to banish your migraines:

<https://blog.themigrainereliefcenter.com/4-online-tools-to-banish-your-migraines>



Thank You

Tmallick@stanfordhealthcare.org

@tmallic

<https://www.linkedin.com/in/theresa-mallick-searle>



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