MIGRAINE PRIMER – NEW TREATMENTS

March 22, 2024

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Disclosures

NONE

Objectives

- 1) Present information for the prevalence and impact of migraine
- 2) Identify patients with migraine based on symptomatology and diagnostic criteria
- 3) Implement evidence-based strategies for the treatment and prevention of episodic and chronic migraine
- 4) Utilize efficacy and safety evidence to identify the appropriate role of new and emerging therapies for patients with migraine

Migraine is an extraordinarily prevalent neurological disease

1) 39+ million women, men and children in the U.S. and 1 billion worldwide are affected by migraine

2) Migraine is the 3rd most prevalent illness in the world.

3) 12-13% of the population – including children – suffers from migraine.

4) 18% of American women, 6% of men, and 10% of children experience migraines.

5) Migraine is the 6th most disabling illness in the world, and 2nd in Yearly Days of Disability.

6) Approximately 1.2 million ER visits are for head pain or acute migraine attacks.

7) More than 4 million people have chronic migraine, with at least 15 migraine days per month.

8) More than 90% of sufferers are unable to work or function normally during their migraine.

Migraine is a public health issue with serious social and economic consequences

1) Healthcare and lost productivity costs associated with migraine are estimated to be as high as $36 billion annually in the U.S.
2) In 2015, the medical cost of treating chronic migraine was more than $5.4 billion, however, these sufferers spent over $41 billion on treating their entire range of conditions
3) Healthcare costs are 70% higher for a family with a migraine sufferer than a non-migraine affected family
4) More than 160 million workdays are lost each year in the US due to migraine
5) U.S. headache sufferers receive $1 billion worth of brain scans each year
6) Beyond the burden of a migraine attack itself, having migraine increases the risk for other physical and psychiatric conditions

Diagnostic criteria for migraine without aura

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours [when untreated in adults]

C. Headache has at least two of the following characteristics:

1.unilateral location

2.pulsating quality

3.moderate or severe pain intensity

4.aggravation by or causing avoidance of routine physical activity

D. During the headache, at least one of the following [is present]:

1.Nausea and/or vomiting

2.Photophobia and phonophobia

E. Not attributable to another disorder

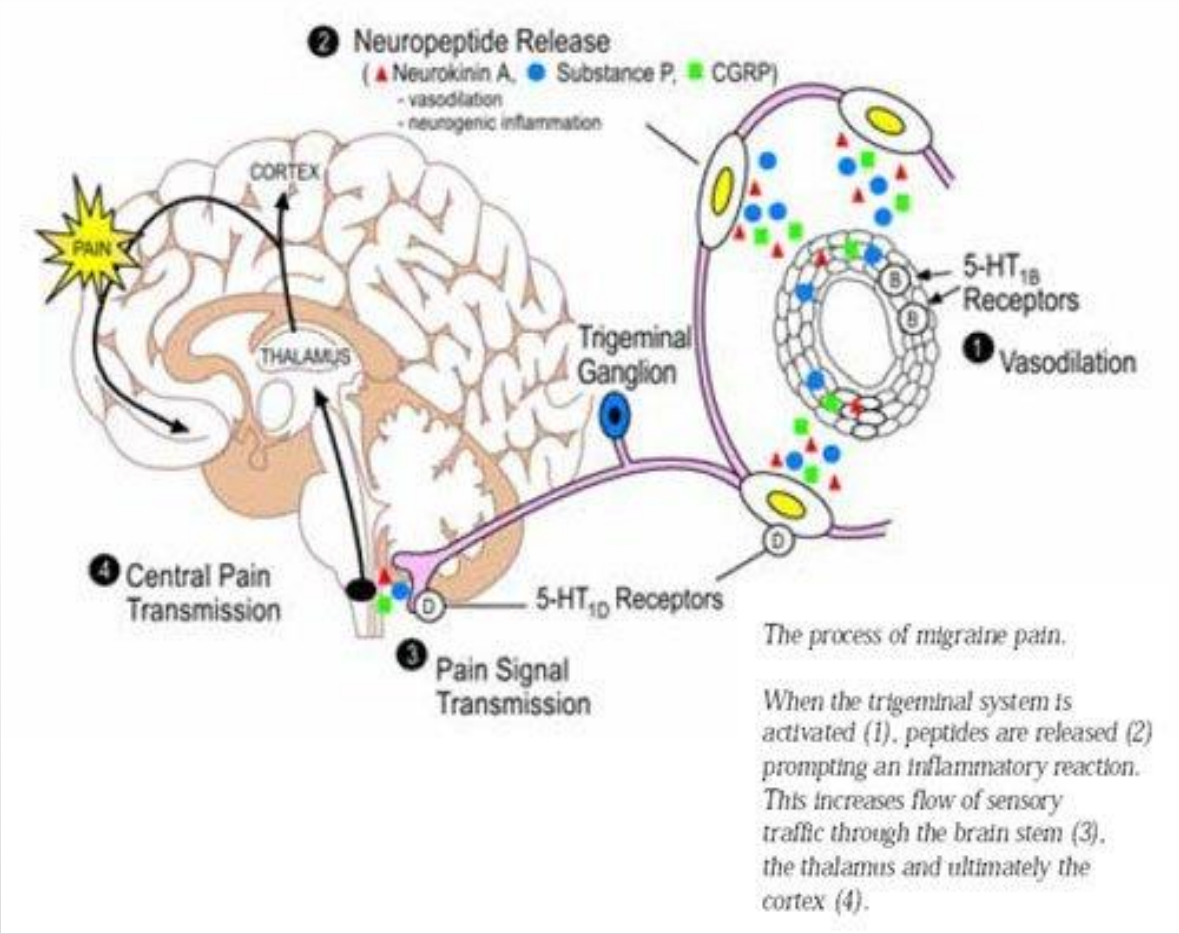
ICHD – 3 (International Headache Society)

Migraine Pathophysiology

Hypothalamus
- Activation in premonitory phase
- Premonitory symptoms
- Target for hypothalamic peptides and modulators

Upper cervical nerves
- Pain transmission or sensitization
- Neck and head pain
- Target for local injections and neuromodulation

Cortex
- Cortical spreading depolarization, altered connectivity
- Migraine aura and cognitive symptoms
- Target for neuromodulation

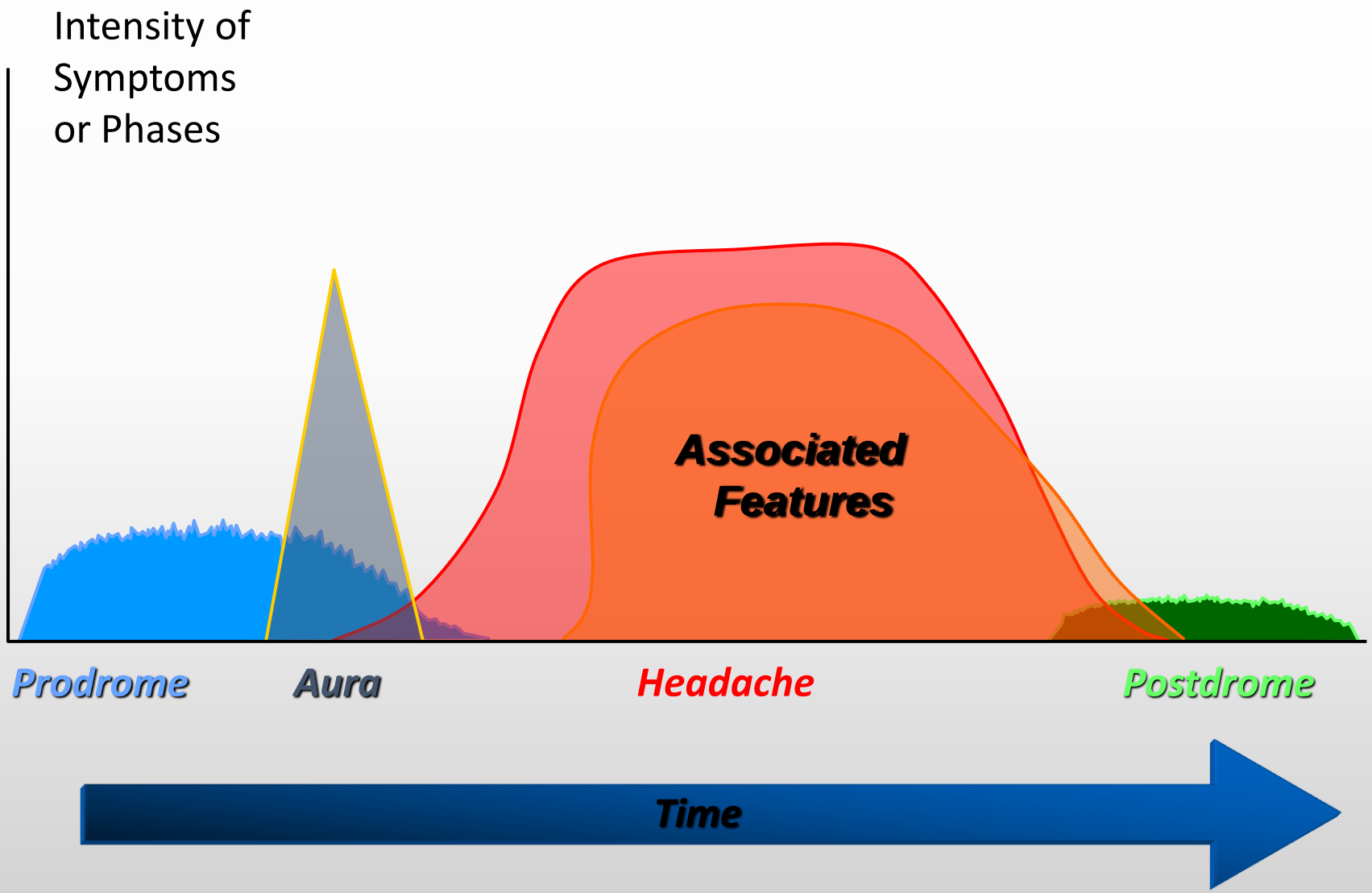


Thalamus
- Sensitization of alteration of thalamo-cortical circuits
- Sensory sensitivity and allodynia
- Target for neuromodulation

Trigemino-cervical complex
- Pain transmission or sensitization
- Headache and neck pain
- Target for medications and neuromodulation

Release of CGRP
- Multiple potential sources or sites of action
- Headache and other symptoms
- Target for small-molecule antagonists and antibodies

The Migraine Attack



ID MIGRAINE

When you have a headache:

Have you felt nauseated or sick to your stomach?

Has light bothered you a lot more than usual?

Have your headaches limited your ability to work, study or do what you needed to do for at least one day?

Yes to 2 out of 3 of these questions is diagnostic for migraine 93% of the time

Lipton, RB, et.al Neurology. 2003 Aug 12;61(3):375-82

Other headache disorders

Tension Headache

A. At least 10 episodes occurring on <1 d/mo on average (<12d/y) and fulfilling criteria B-D
B. Headache lasting 30min-7d
C. headache has at least 2 of the following characteristics:
1. Bilateral location
2. Pressing/tightening (nonpulsating) quality
3. Mild or moderate intensity of pain
4. Not aggrevated by routine physical activity (e.g., walking or climbing stairs)
D. Both of the following:
1. No nausea or vomiting (anorexia may occur)
2. No more than 1 of photophobia or phonophobia
E. Not attributed to another disorder

Headache due to Rhinosinusitis

A. Frontal headache accompanied by pain in 1 or more regions of the face, ears, or teeth and fulfillingg criteria C and D
B. Clinical, nasal endoscopic, CT, and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis
C. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis
D. Headache and/or facial pain resolve within 7d after remission or successful treatment of acute or acute-on-chronic rhinosinusitis

Adapted from Headache Classification Subcommittee of the International Headache Society)

Other Headache Disorders

Cluster Headache

A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 min if untreated
C. Headache is accompanied by at least 1 of the following:
  1. Ipsilateral conjunctival injection and/or lacrimation
  2. Ipsilateral nasal congestion and/or rhinorrhea
  3. Ipsilateral eyelid edema
  4. Ipsilateral forehead and facial sweating
  5. Ipsilateral miosis and/or ptosis
  6. Sense of restlessness or agitation
D. Attacks have a frequency of 1 every other day to 8/d
E. Not attributed to another disorder

(*Adapted from* Headache Classification Subcommittee of the International Headache Society)

Worrisome Headache Red Flags

"S(S)NOOP"

Systemic symptoms (fever, weight loss) or
Secondary risk factors (HIV, systemic cancer)

Neurologic symptoms or abnormal signs (confusion, impaired alertness, or consciousness, hemiparesis)

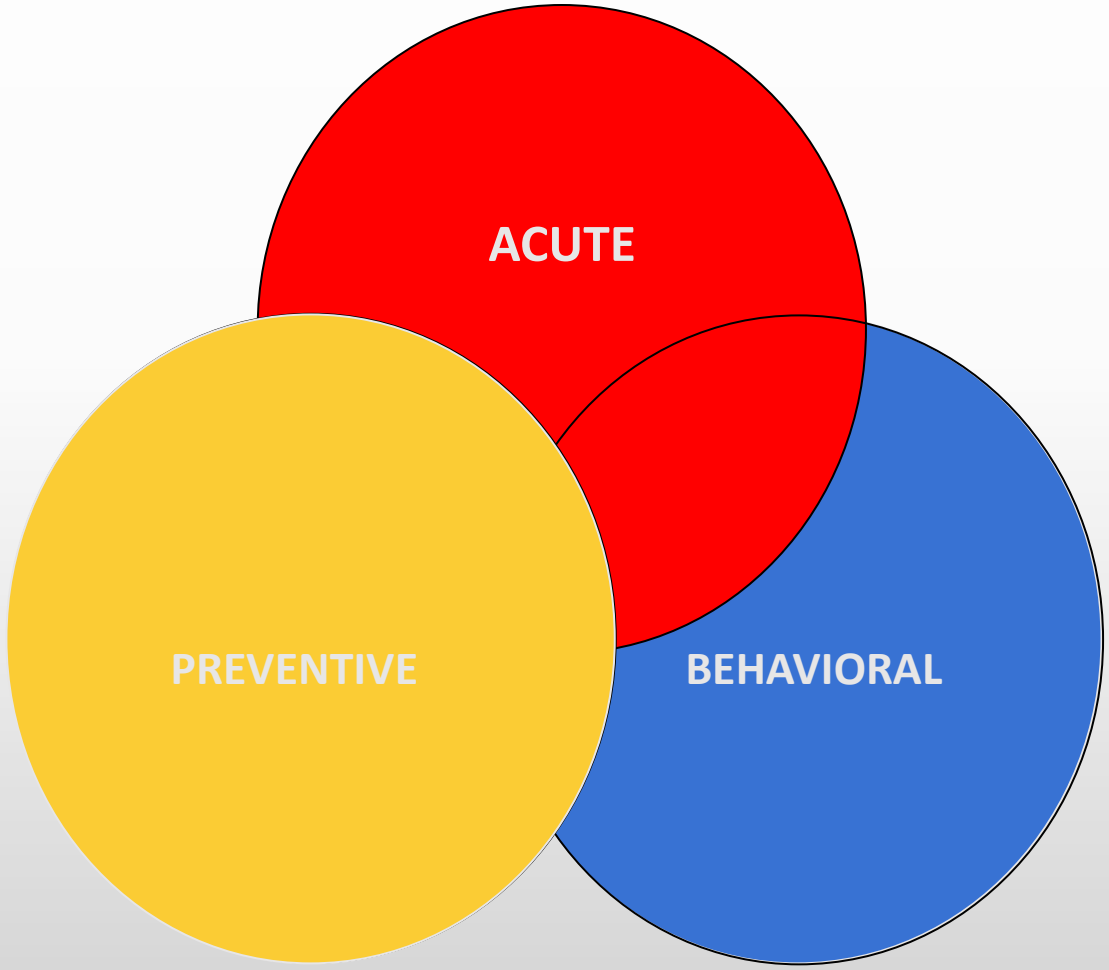
Onset: sudden, abrupt, or split-second

Older: new onset and progressive headache, especially in middle age >50 (giant cell arteritis)

Previous headache history: first headache or different (change in frequency, severity or clinical features)

Dodick DW. *Adv Stud Med*. 2003;3(6C):S550-S555.

Integrated Treatment Approach



ACUTE MEDICATION TREATMENTS

Acute Treatment of Migraine

TRIPTANS	ERGOTS	NON-SPECIFIC TREATMENTS
Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Sumatriptan Suma + naproxen Zolmitriptan	Dihydroergotamine (Migranal, Trudesa) Ergotamine + caffeine	Antiemetics Aspirin +/– acetaminophen +/– caffeine Diclofenac, ketorolac, other NSAIDs Corticosteroids (IV; rescue therapy)

A variety of routes of administration (eg, oral, nasal spray, suppository) and combinations are available

- Products containing butalbital are sometimes used despite evidence that butalbital is not effective for migraine pain and can cause rebound headache
- Reserve opiates only for limited use in very severe migraine

Med Lett Drugs Ther. 2017;59:27-32.

New Acute Migraine Medications

CGRP receptor antagonists – Gepants

Ubrogepant (Ubrelvy) 50 – 100 mg

Rimegepant (Nurtec ODT) 75 mg

Zavegepant (Zavzepret NS) 10 mg

} block action of CGRP on receptors

Side effects: nausea, dizziness, fatigue, dry mouth, dysgeusia (zavzepret)

Selective Serotonin5-HT$_{1F}$ - Ditans

Reyvow (Lasmiditan) 50, 100, 200 mg

(Do Not Drive or Operate Machinery for 8 hours)

activate 5-HT 1F receptor to modulate pain signaling without vasoconstriction

Side effects: Dizziness, fatigue, sleepiness, N/V

New Acute Migraine Medications

Ubrogepant

Dosage

The recommended dose is 50 mg or 100 mg taken orally, as needed. If needed, a second dose may be administered at least 2 hours after the initial dose. The maximum dose in a 24-hour period is 200 mg.

Rimegepant

Dosage

The recommended dose is 75 mg. Can be placed on or under the tongue to dissolve and then swallowed. Only one dose per 24 hours

Zavzepret

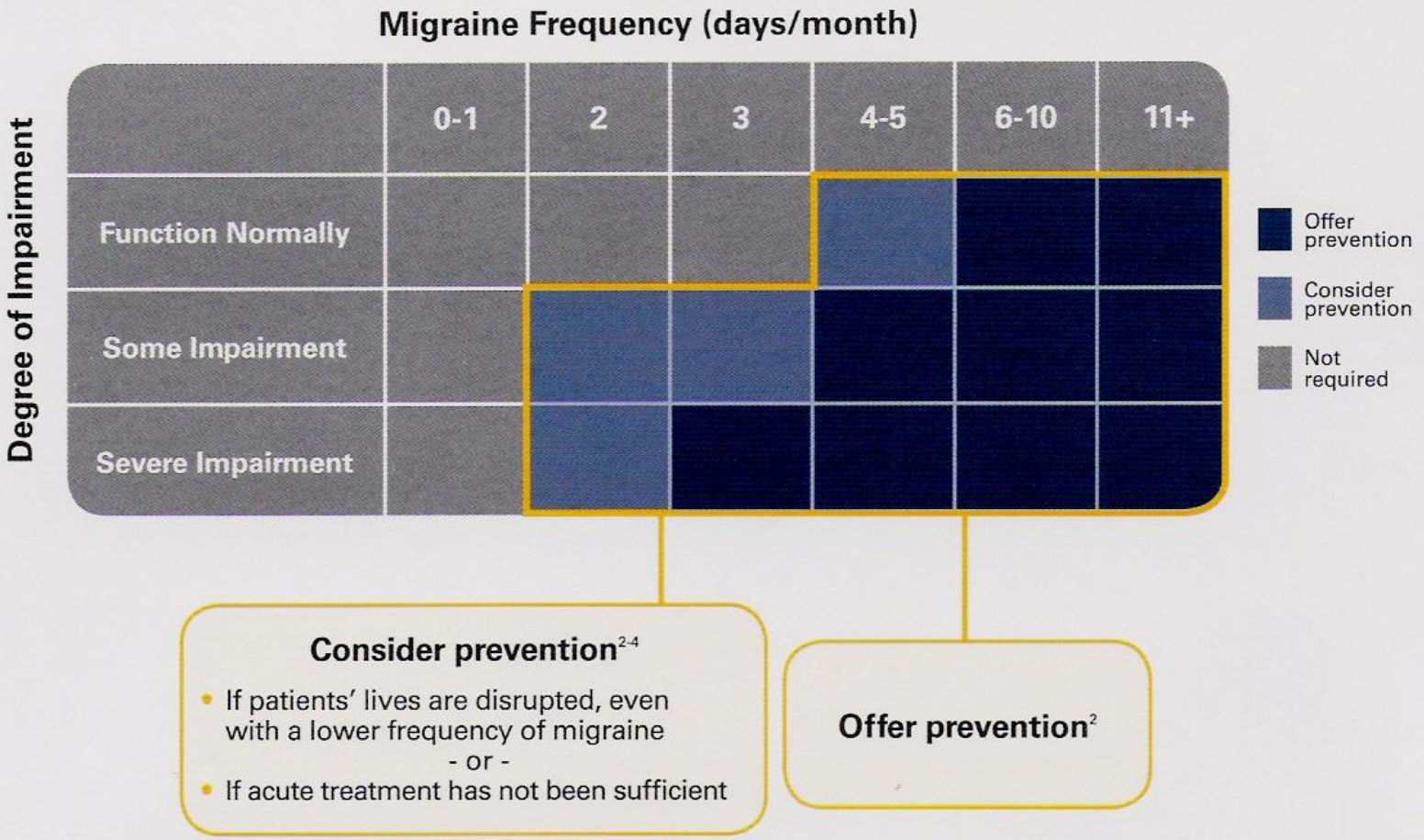
Dosage

The recommended dose is 75 mg. Can be placed on or under the tongue to dissolve and then swallowed. Only one dose per 24 hours

PROPHYLACTIC TREATMENTS

Recommendations for migraine care[2,3]

- Expert consensus by key opinion leaders urges consideration of both the **frequency of migraine** and **degree of impairment** when determining if patients are right for migraine prevention



AAN/AHS Classification of Non-specific Preventive Therapies for Episodic Migraine

Level A: Medications With Established Efficacy (≥2 Class I Trials)

Antiepileptic drugs
Divalproex sodium
Valproate sodium
Topiramate

β-Blockers
Metoprolol
Propranolol
Timolol

Triptans (MRM)
Frovatriptan*

Level B: Medications That Are Probably Effective (1 Class I or 2 Class II Studies)

Antidepressants/SSRI/SSNRI/TCA
Amitriptyline
Venlafaxine

β-Blockers
Atenolol
Nadolol

Triptans (MRM)
Naratriptan*
Zolmitriptan

Level C: Medications Possibly Effective (1 Class II Study)

ACE inhibitors
Lisinopril

Angiotensin receptor blockers
Candesartan

α-Agonists
Clonidine
Guanfacine

Antiepileptic drugs
Carbamazepine

Antihistamines
Cyproheptadine

Silberstein SD, et al. *Neurology*. 2012;78:1337-1345.

FDA-Approved Preventive Therapies for Migraine

Anti-CGRP monoclonal antibodies*

Erenumab, Fremanezumab, Galcanezumab, Eptinezumab

OnabotulinumtoxinA – only approved for chronic migraine

Gepants*

Atogepant, Rimegepant

Other

Topiramate*

Med Lett Drugs Ther. 2017;59:27-32.

*Also FDA approved for prevention of *episodic* migraine

Adverse effects of CGRP MAB's

ERENUMAB	FREMANEZUMAB	GALCANEZUMAB	EPTINEZUMAB
Injection site reaction, hypersensitivity reaction, constipation*	Injection site reaction, hypersensitivity reaction	Injection site reaction, hypersensitivity reaction	Infusion reaction; flushing, hot feeling, scratchy throat, hypersensitivity reaction

BOTOX

- Approved in October 2010 after PREEMPT 1 & 2 RCT
- Used for treatment of Chronic Migraine - >15 days/month
- Given by injection in 31 sites on head and neck
- Potent neurotoxin – blocks communication between nerve and muscle, although in migraine BOTOX may change pain impulses to Trigeminal nerve
- May also block CGRP and decrease or prevent Cortical Spreading Depression
- Typical response lasts for up to 3 months

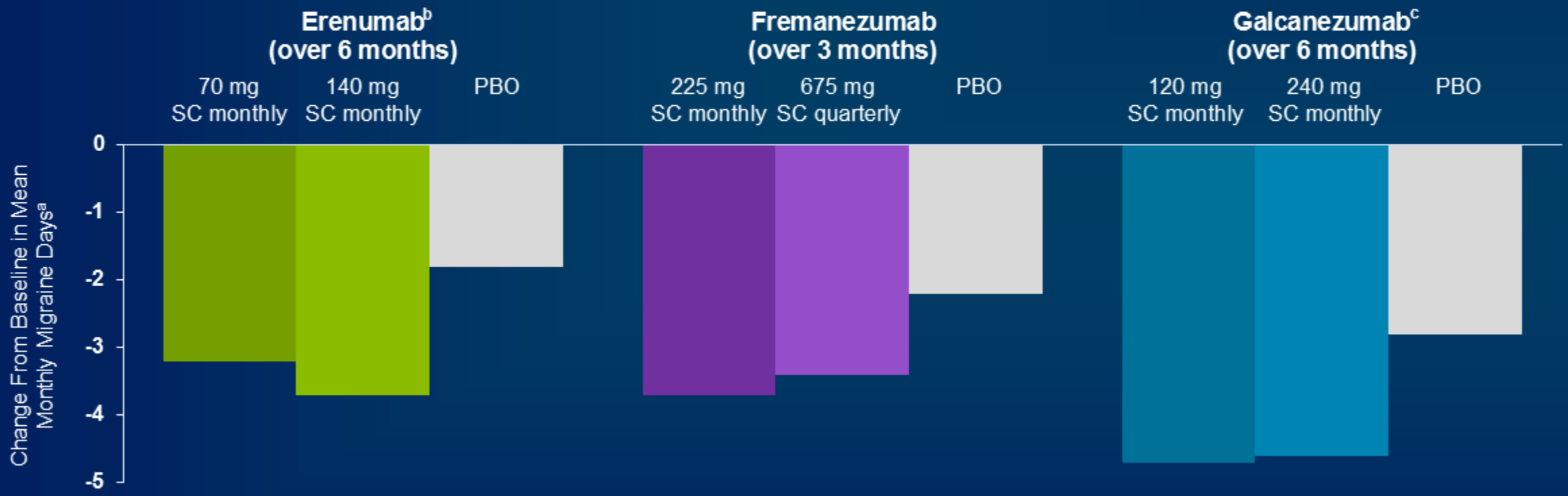
BOTOX

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine vs placebo include, respectively:

neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients

CGRP-Targeted Therapies: Examples of Phase 3 Efficacy Results for Prevention of Episodic Migraine



[a]All active drug doses were statistically better than placebo (PBO); [b]data from erenumab STRIVE study; ARISE study did not use 140 mg dose; [c]data from galcanezumab EVOLVE-1 study (North America); EVOLVE-2 (global) had similar data.

Dodick DW, et al. *JAMA*. 2018;319:1999-2008; Goadsby PJ, et al. *N Engl J Med*. 2017;377:2123-2132; Stauffer VL, et al. *JAMA Neurol*. 2018;75:1080-1088.

2024 American Headache Society Consensus Statement

The CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without a requirement for prior failure of other classes of migraine preventive treatment.

Headache. 2024: 11 March 2024

Devices

Several devices have been approved for treatment of episodic and chronic migraine, for those individuals without benefit, are intolerant of or have a contraindication to typical pharmacological treatments

Supraorbital transcutaneous nerve stimulator – Cefaly; cleared for acute and prophylactic migraine treatment ($300 - $525)
External vagal nerve stimulator – gammaCore; cleared for migraine and cluster headaches ($600+)
Remote Electrical Neuromodulator – Nerivio; cleared for acute and prophylatic migraine treatment (initial $49 for 18 “doses”, refills $99)
Transcranial Magnetic Stimulation – SpringTMS ($200 - $250 per month lease)

Remote Electrical Neuromodulator

Nerivio™ is a wireless remote electrical neuromodulation device for the acute treatment of migraine with or without aura in patients 18 years of age or older.

This prescription device is applied to the upper arm at the onset of migraine headache or aura to stimulate the C and Aδ nociceptive sensory fibers of the upper arm. The message from the arm is received by the brainstem pain regulation center that releases neurotransmitters that inhibit the incoming messages of pain in the trigeminal cervical complex (TCC).

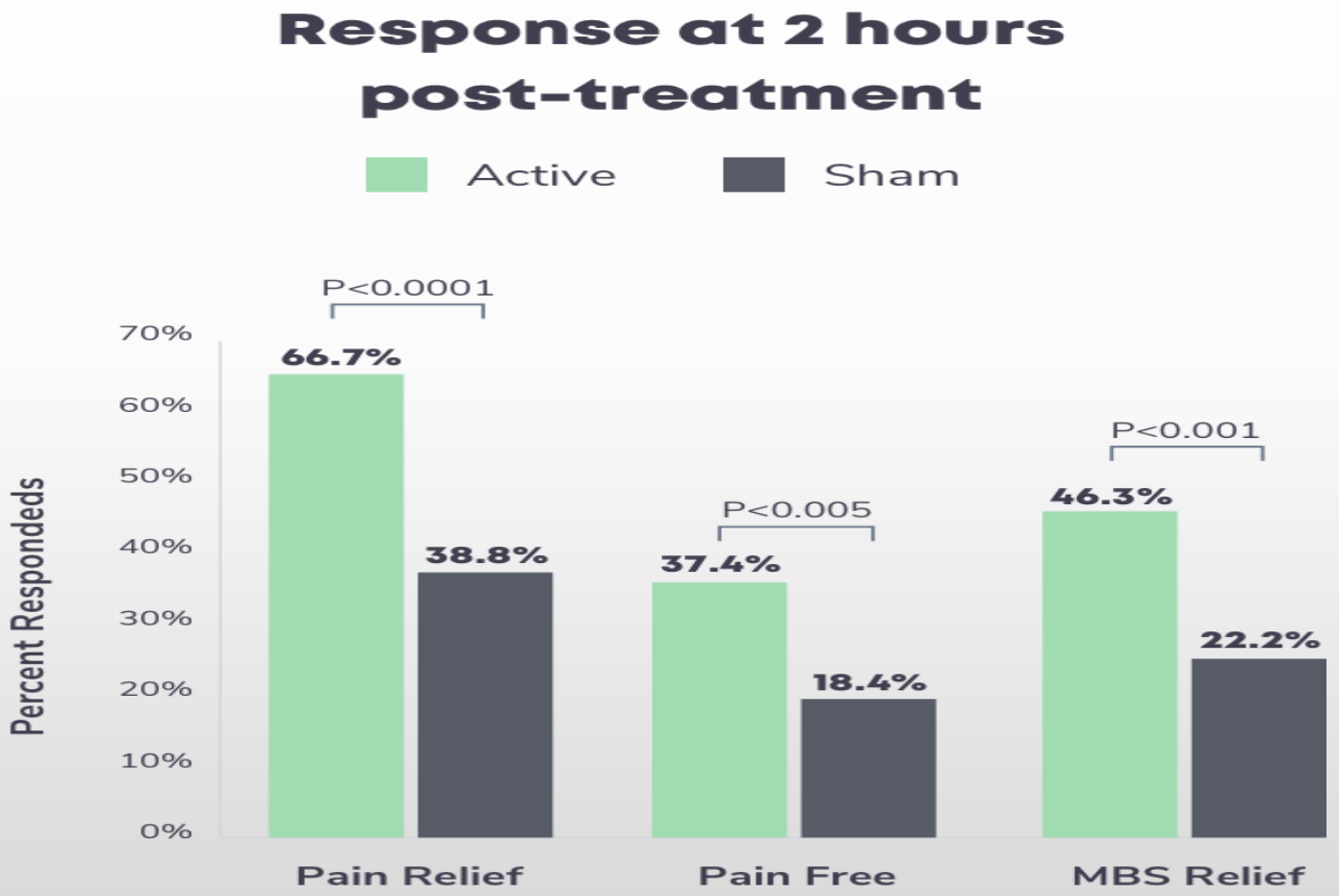
The incidence of device-related adverse events was low (3.6% participants) and similar between treatment groups. The most common adverse effect was feeling of warmth to 1.6% versus the sham device at 0.8%, other symptoms were localized with redness, tingling and arm pain, or at none of the participants withdrew from the study due to adverse events.

Remote Electrical Neuromodulator

66.7% of patients achieve pain relief

37.4% of patients achieve pain freedom

(Yarnitsky at al., Headache, 2019)



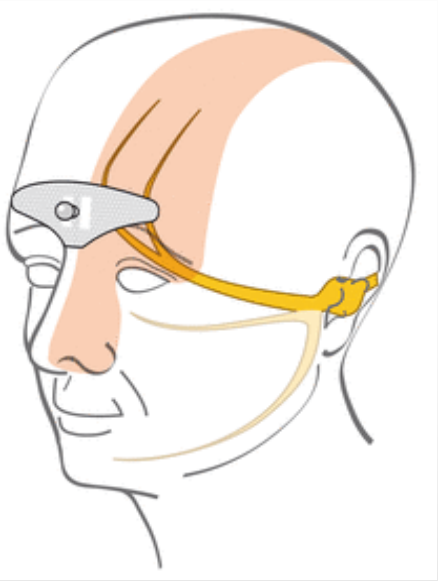
Transcutaneous supraorbital nerve stimulator (tSNS)

Approved for the treatment of acute episodic and chronic migraines

Acute migraine treatment (1-hour session)

Significant pain relief for 8 out of 10 patients

Total Pain freedom for one third of patients



Migraine Prevention (daily 20-minute sessions)

Migraine attack reduction - 54%

Medication intake reduction - 75%

Transcutaneous supraorbital nerve stimulator (tSNS)

The side effects of tSNS

- Observed in 4.3% of patients
- Mild and completely reversible
- Most common: intolerance to the feeling of the device on the forehead
- Most severe: allergic skin reaction to the electrode

The most common side effects

- Sensation of fatigue during and after the session: 0.65%
- Intolerance to the feeling of Cefaly on the forehead: 1.25%
- Headache after one session: 0.52%
- Irritation of the skin on the forehead: 0.22%

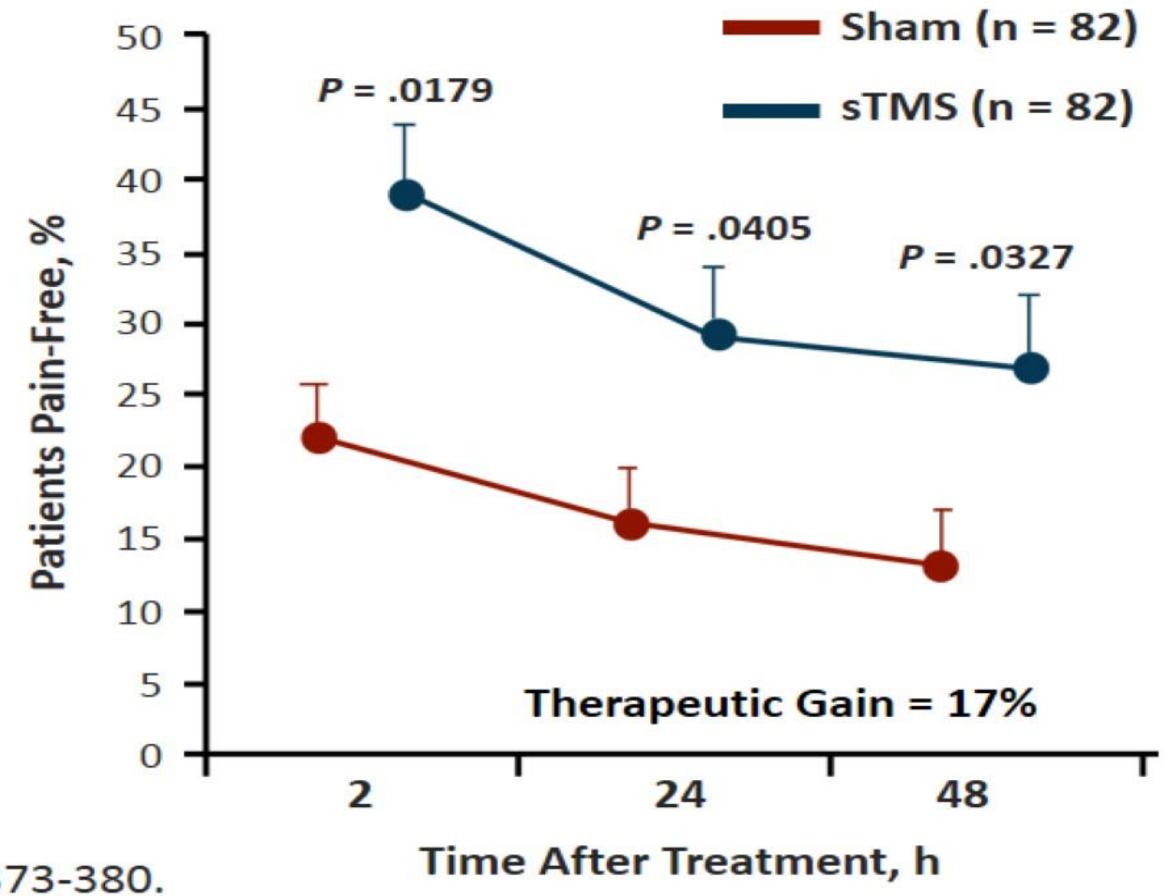
Development of a Noninvasive Vagus Nerve Stimulator

- This is a handheld, patient-controlled nVNS device
  - Produces a uniform electric field across the surface of the electrodes
  - Selectively stimulates low-threshold myelinated afferent A fibers, but not higher-threshold C fibers
  - Delivers 90-second stimulations that can be used repeatedly

Oshinsky ML, et al. *Pain*. 2014.155:1037-1042.
Silberstein S, et al. *Headache*. 2014;54:1426-1427. Abstracts LBP 19, 21.

sTMS RCT for Acute Treatment of Migraine With Aura (≥ 30% of Attacks)

SpringTMS



Lipton RB, et al. *Lancet Neurol.* 2010;9:373-380.

Key Points

Migraine is a very common disorder causing severe, although often temporary disability

Using diagnostic criteria or brief screeners enhances the appropriate diagnosis

There are several acute treatments available including medications and devices. New acute medications may be useful for those individuals who cannot tolerate or have contraindications for presently available treatments.

New prophylactic medicines have the potential to improve migraine treatment with fewer side effects and better compliance

Rare Headache Disorders

	Epicrania fugax	Nummular headache	Primary stabbing headache	SUNCT/SUNA	Occipital neuralgia
Site	Posterior parietal	Parietal	Temporal	Orbital, periorbital, temporal	From neck to vertex
Location	Linear spread	Circular area (1–6 cm)	Multiple	Unilateral	Along the greater, lesser and third occipital nerves
Duration	1–10 seconds	Minutes to hours to days	Few seconds	1–600 seconds	Few seconds
Intensity	Moderate	Mild to moderate	Severe	Severe	Severe
Character	Current like	Variable	Stabbing	Saw tooth attacks	Stabbing, electric
Associated features	Occasional	None	None	Autonomic symptoms 100%	None
Triggers	Usually spontaneous occasionally has triggers	None	None	Multiple	Trigger points—emergence of greater occipital nerve or distribution of C2

THANK YOU

?????? QUESTIONS ??????