PainWeek®

Neuroregulation: Keeping Your Brain Tidy

Carol A. Barch, MN, FNP-BC, AQH

Disclosure

- Advisory Board: Theranica

Learning Objectives

- Review migraine disorder and pathophysiology
- Define neuromodulation and relationship to migraine control
- Discuss the strategies and devices that may be used to promote neuromodulation and ultimately migraine control.

Headaches

Primary Headache

- Migraine
  - Episodic < 14 headache days a month
  - Chronic > 15 headache days a month
- Tension Type Headache (TTH)
- Trigeminal autonomic cephalalgia
  - Cluster
  - Paroxysmal hemicrania
  - Short lasting unilateral neuralgiform (SUNCT)
- Other -
  - Primary stabbing headache
  - Hypnic headache
  - Primary cough headache
  - Exercise (exertional) headache
  - Headache associated with sexual activity

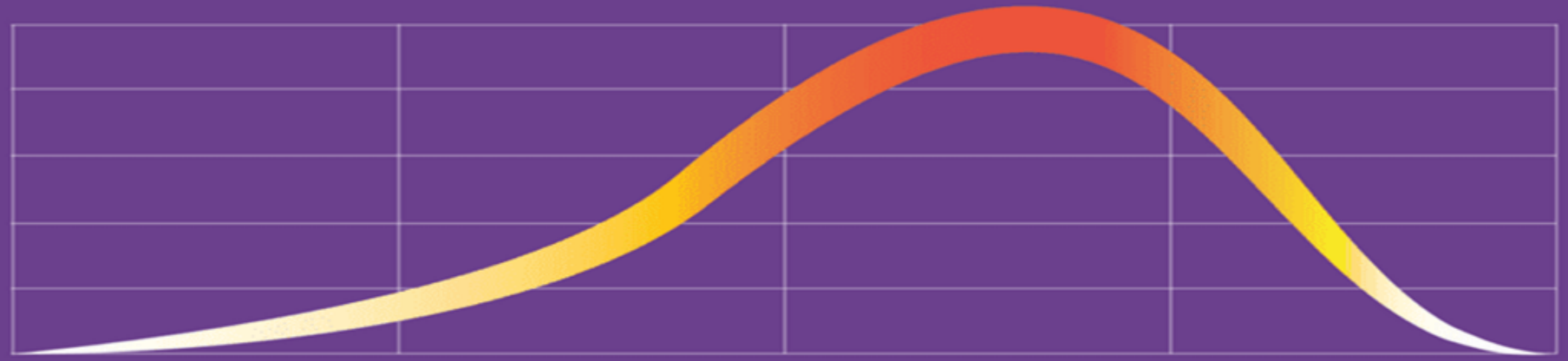
Secondary Headaches

- Sub arachnoid hemorrhage (SAH)
- Stroke
- Brain Tumor
- Infectious process
- Viral

Migraine

- > 37 million people with migraine in the US
- Not well understood, poorly identified, poorly treated, and stigma
- Whole Brain Disorder
- Occurs throughout the life span
- Disability
- Management costs are high

TIMELINE OF A MIGRAINE ATTACK



PRODROME
FEW HOURS TO DAYS

- IRRITABILITY
- DEPRESSION
- YAWNING
- INCREASED NEED TO URINATE
- FOOD CRAVINGS
- SENSITITIVY TO LIGHT/SOUND
- PROBLEMS IN CONCENTRATING
- FATIGUE AND MUSCLE STIFFNESS
- DIFFICULTY IN SPEAKING AND
- READING
- NAUSEA
- DIFFICULTY IN SLEEPING

AURA
5-60 MIN

- VISUAL DISTURBANCES
- TEMPORARY LOSS OF SIGHT
- NUMBENESS AND TINGLING ON PART OF THE BODY

HEADACHE
4-72 HRS

- THROBBING
- DRILLING
- ICEPICK IN THE HEAD
- BURNING
- NAUSEA
- VOMITING
- GIDDINESS
- INSOMNIA
- NASAL CONGESTION
- ANXIETY
- DEPRESSD MOOD
- SENSITIVITY TO LIGHT, SMELL, SOUND
- NECK PAIN AND STIFFNESS

POSTDROME
24-48 HRS

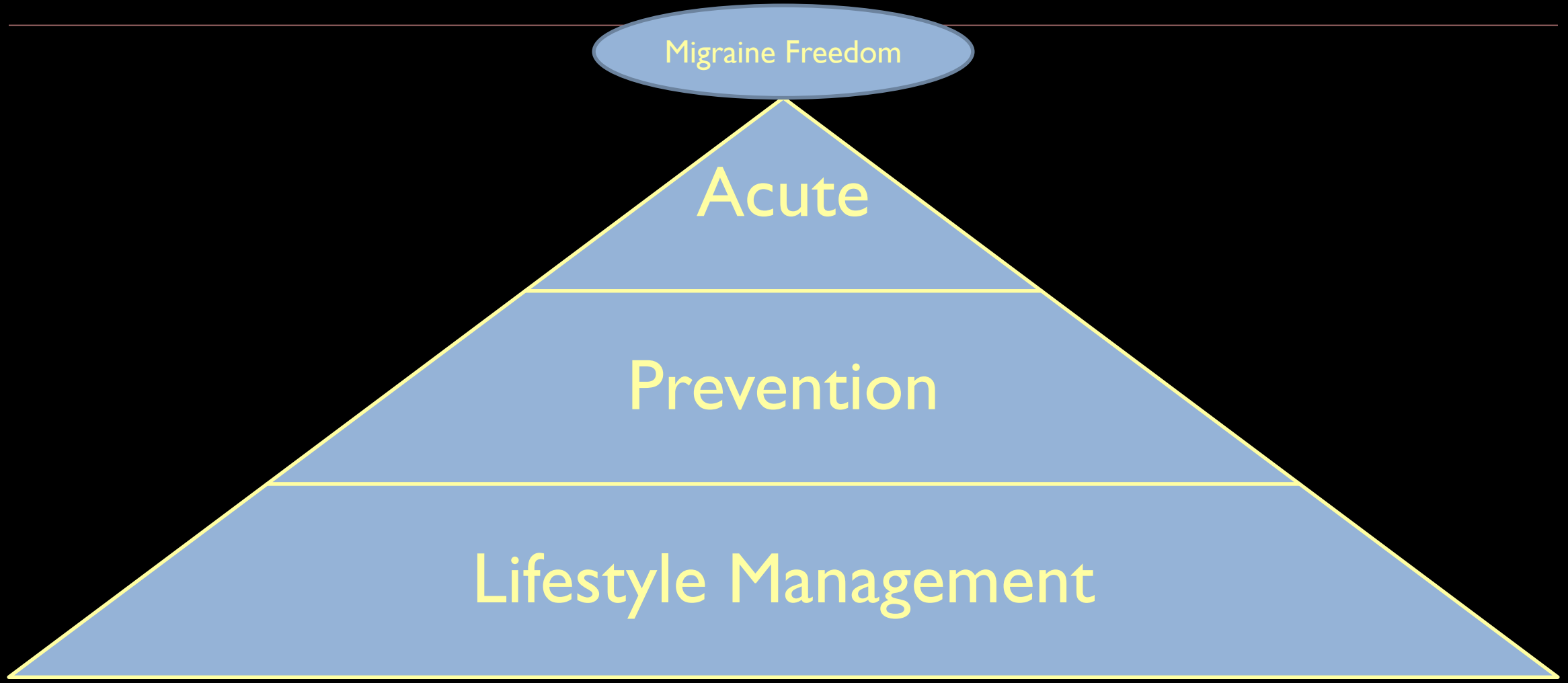
- INABILITY TO CONCENTRATE
- FATIQUE
- DEPRESSED MOOD
- EUPHORIC MOOD
- LACK OF COMPREHENSION

Migraine as defined by the International Classification of Headache Disorders, third edition (ICHD-3), should include the following:

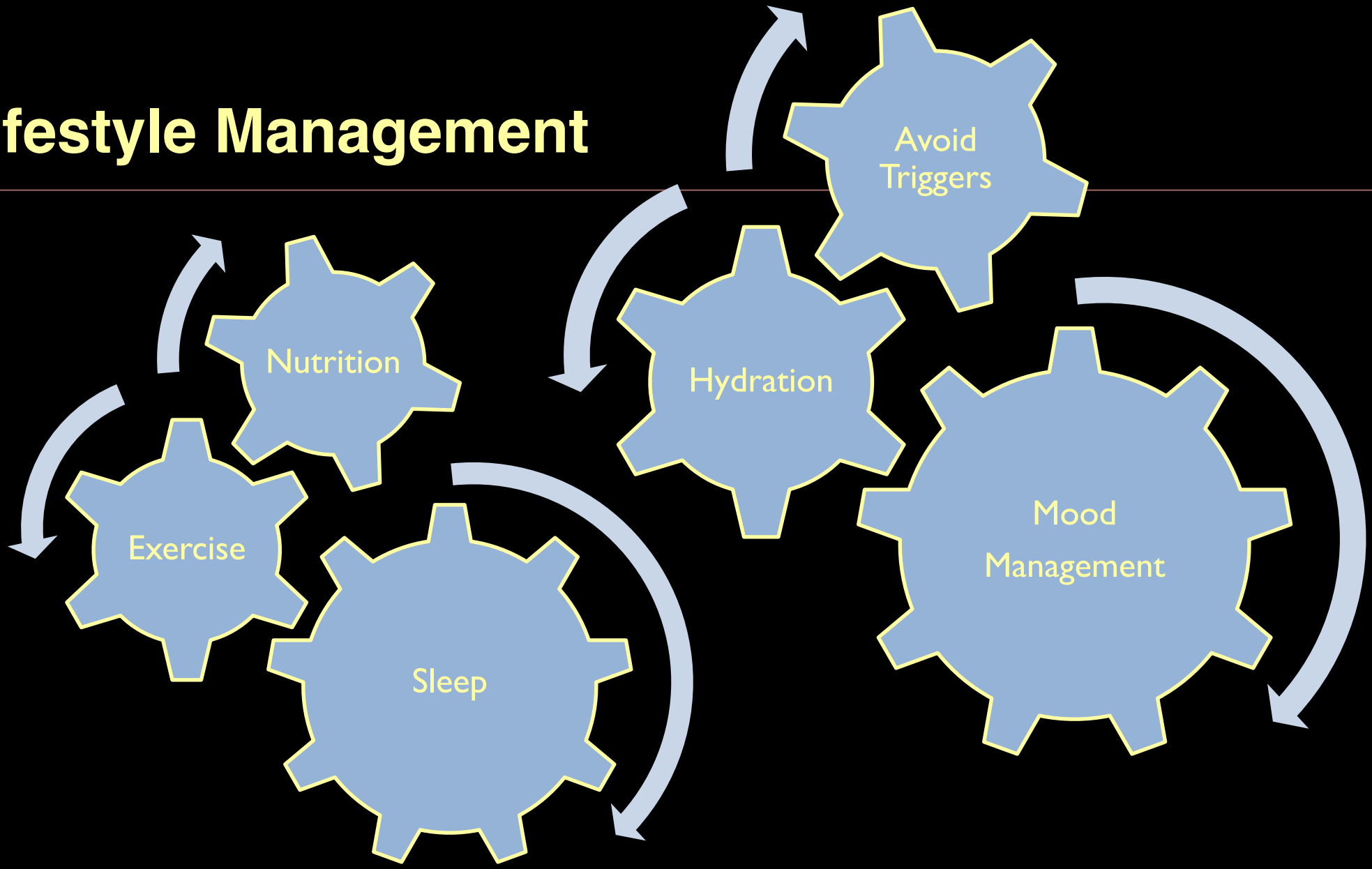
- At least 5 attacks or more in lifetime
- Headache lasting 4-72 hours
- May last 2-72 in children
- Patients should experience at least 2 of these pain characteristics
  - Unilateral (bilateral more often in children)
  - Pulsating quality moderate to severe intensity
  - Aggravated by routine physical activity
- And at least 1 of the following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia (may be inferred by behavior in children)
- Not better accounted for by another ICHD diagnosis

- Migraine with aura :At least 2 attacks with
- 1 or more of the following fully reversible aura symptoms
  - Visual
  - Sensory
  - Speech and /or language
  - Motor
  - Brainstem
  - Retinal
- And at least 3 of the following:
  - At least one aura symptom spreads > 5 min
  - Two or more symptoms in succession
  - Each aura symptom lasts 5- 60 minutes
  - 1 unilateral
  - At least 1 aura symptom is postivite
  - aura is accompanied or followed with 60 minutes of headache.
- Not better accounted for by another ICHD diagnosis

Management of Migraine



Lifestyle Management



Prevention – consider > 4 headache days a month

- Non-pharmacological approaches
- Nutraceuticals
- Oral Medications
- Calcitonin Gene Related Peptides (CGRP) monoclonal antibodies
- OnobotulinumtoxinA - Chronic Migraine
- Neuromodulation*

Acute Attacks

- NSAIDs
- Tripans
- GPANTS
- DITANs
- Anti-emetics
- Neuromodulation*

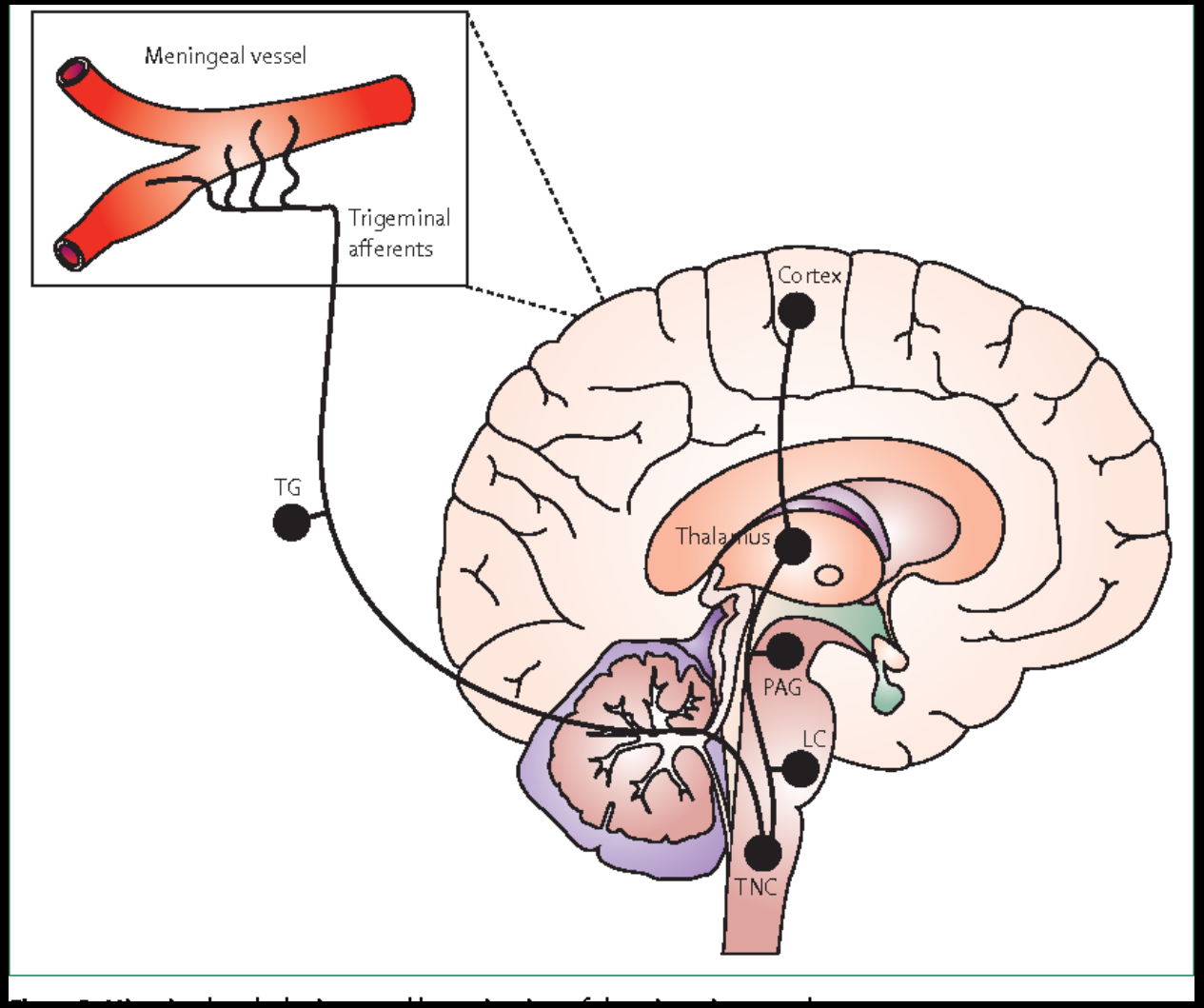
Neuromodulation

The International Neuromodulation Society defines therapeutic neuromodulation as “the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.” – by modulating abnormal neural pathway behavior caused by the disease process, profound effects occur including relief of pain, restoration of function.

In appropriate patients, this growing class of therapies, in common use since the 1980s, can help restore function or relieve symptoms that have a neurological basis.

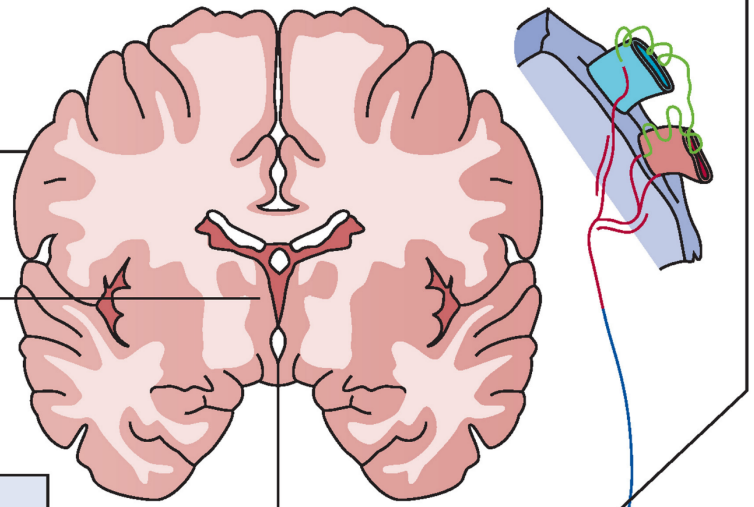
Migraine Pathophysiology

- Cortical spreading depression
  - Cause of aura of migraine
  - Activates trigeminal nerve afferents
- Trigeminovascular system activation
  - Trigeminal ganglion and Upper cervical roots activates large cerebral vessels pia vessels
  - and trigeminal nucleus caudalis fibers involved in localization of pain signals to thalamus and then to cortex
  - Neurogenic inflammation prolongs and intensifies pain elevated levels of neuropeptides activating the trigeminal system



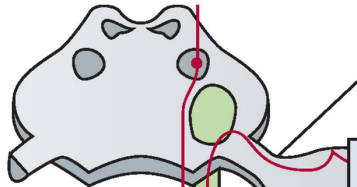
Cortex
Cortical spreading depolarisation, altered connectivity
Migraine aura and cognitive symptoms
Target for neuromodulation

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

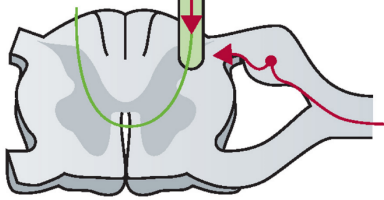


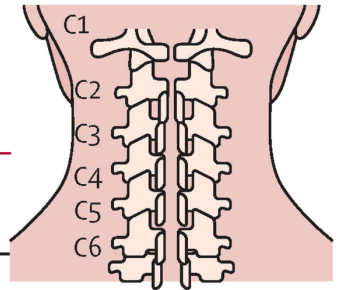
Thalamus
Sensitisation and alteration of thalamo-cortical circuits
Sensory sensitivity and allodynia
Target for neuromodulation

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



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





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

Neuromodulation Devices

External devices –FDA approved

- E-TNS – an external trigeminal nerve stimulator (Cefaly)
- nVNS – a noninvasive vagal nerve stimulator (Gammacore)
- sTMS - a single – pulse transcranial magnetic stimulator (sTMS mini)
- REN – a remote electrical neuromodulator (Nerivio)

Implanted devices

- Occipital nerve stimulation
  - Medtronic
  - St. Judes
  - Boston Scientific
- Subraorbital nerve stimulation
- Vagus nerve stimulation

- Should only be used where patients are refractory to other preventatives including non-invasive methods
  - Minimally invasive Occipital Nerve Stimulation for Trigeminal Autonomic Cephalgia (TAC)

    Has been studied in intractable cluster, SUNCT/SUNA, hemicrania continua (50-80% cumulative response, open label, small samples)

ETNS (Cefaly)

Dual device

- Acute setting: at onset of attack use for 1 hr
- Prevention Settings: once daily for 20 minutes

ETENS: Side effects and Contraindications

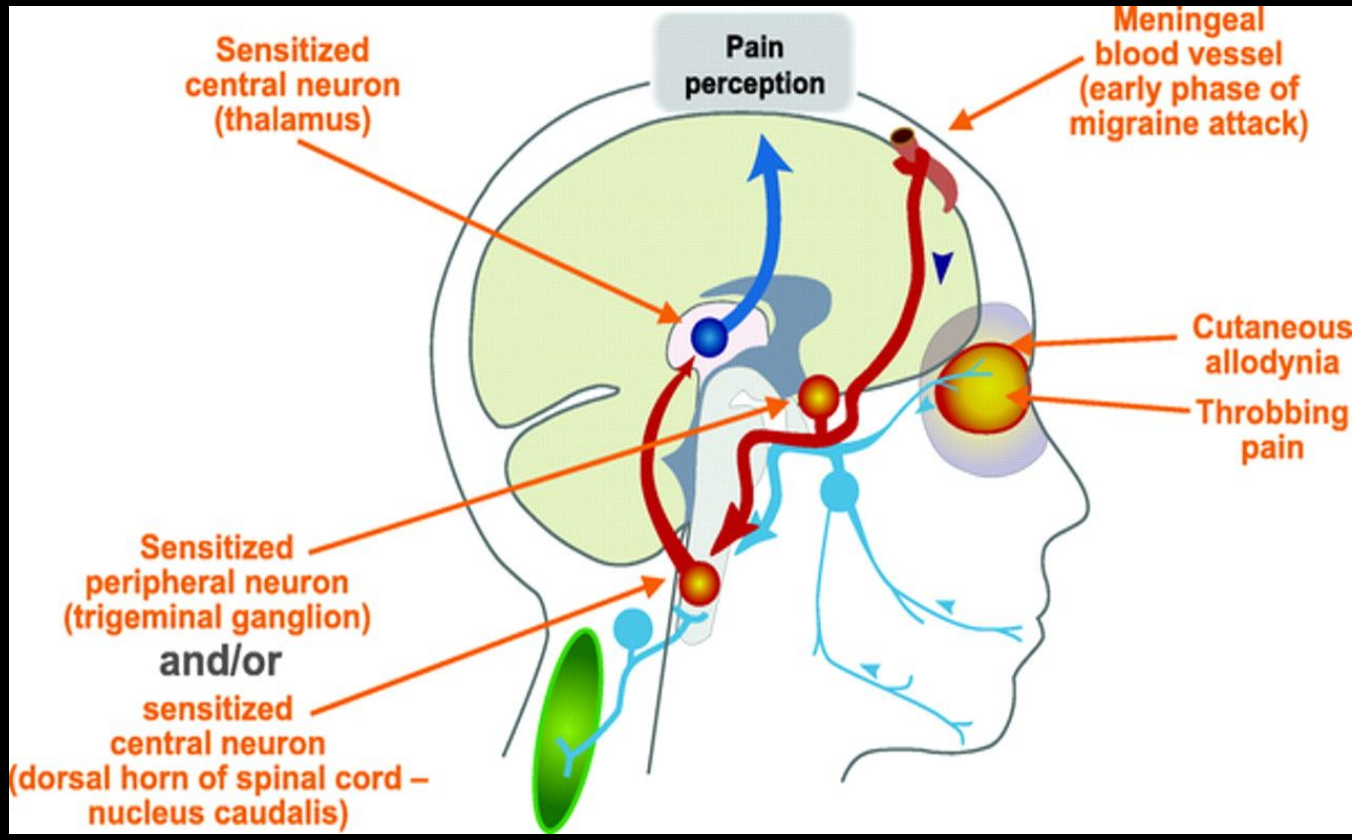
- **Side Effects:**
  - can cause irritation at the application site, fatigue – painful due to allodynia

- **Do Not Use CEFALY if**
  - implanted metallic or electronic device in the head.
  - cardiac pacemaker or implanted or wearable defibrillator.
  - pregnant or may become pregnant.
  - suspect or known heart problems.
  - recent head injury.
  - seizure.

- **Warnings**
  - Do not use CEFALY DUAL while sleeping.
  - Do not use CEFALY DUAL in a wet environment, such as in the bath or shower.
  - Do not use CEFALY DUAL while driving, operating machinery, or during any activity that requires you to be alert and focused. Wait for 1 hour after each treatment session before resuming any such activity.
  - The CEFALY DUAL and electrodes are designed for and should be used only in the forehead region.
  - Do not use CEFALY DUAL in the neck region.
  - While CEFALY DUAL's design prevents this, do not use CEFALY DUAL close to the thorax (chest region).
- Use CEFALY DUAL only on normal, intact and clean skin.
  - Use caution or avoid using CEFALY DUAL if there has been any loss of feeling in the skin of your forehead or scalp until the normal feeling is resumed.
  - Use CEFALY DUAL only with the electrodes and accessories recommended by CEFALY Technology.
  - If you have known allergies to acrylates, contact CEFALY Technology for hypoallergenic electrode alternatives.

eTNS: pathophysiolgy

- External trigeminal nerve stimulator
  - The actual mode of action is not known
  - May modulate PNS by stimulation of supraorbital nerve. This modulates pain transmission via action on the trigeminovascular system.
  - setting stimulates the trigeminal nerve producing a sedative effect on the nervous system that may relieve headache pain



Clinical Evidence: ETNS (Cefaly)

Study	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy	Safety
STNS EM with/without Aura	RCT	Once daily treatment for 20 minutes	67	Reduction monthly migraine days: 6.94-4.88 days (P=.023) in treatment No change in Sham 50% responder rate 38.1% (P=.23) in treatment arm	Well tolerated
STNS CM prevention	Open Label Prospective	Once daily treatment for 20 minutes	23	Baseline Headache days 20.7 =/-5.7 days/month Baseline acute medication use 20.2+/-12.4 times/month 8 patients achieved both primary end points 7.6 headache days /month at month 4 6.3 times/month acute medication use at month 4	In the treatment group, (3) subjects were unable to tolerate the device due to neck pain (1), worsening headache (1) unable to tolerate paresthesia
STNS Acute Migraine Therapy ACME trial	RCT	STNS used for 1 hour at the onest of migraine attack	106	Mean change in pain intensity at 1 hour compared to baseline: -3.46 +/-2.32 with STNS vs 1.78+/- 1.89 with sham (P<0001)	Well tolerated In the treatment group, (4) subject were unable to tolerate the paresthesia sensation, and (1) developed nausea during treatment

nVNS (Gammacore)

- Migraine Prevention: apply two 120 second stimulations TID
  - first dose within 1 hour of awaking the second dose 4-6 hours after the 1st dose and at night
- Acute Migraine Treatment at onset of migraine pain Apply two 120 second stimulations, 20 minutes later may repeat, wait 2 hours from the start of first treatment and may repeat the two 120 second stimulations.

- Episodic Cluster: Three 120 second stimulations wait 3 minutes may repeat Three 120 second stimulations.
- May treat up to 4 attacks (8 treatments) for total of 24 stimulations per day.

vVNS: Side effects and Contraindications

The most common side effects of gammaCore include:

- Discomfort, redness, or tingling at the application site
- Dizziness
- Local pain or muscle twitching in the face/head/neck area

gammaCore is not indicated for anyone who is pregnant or people with:

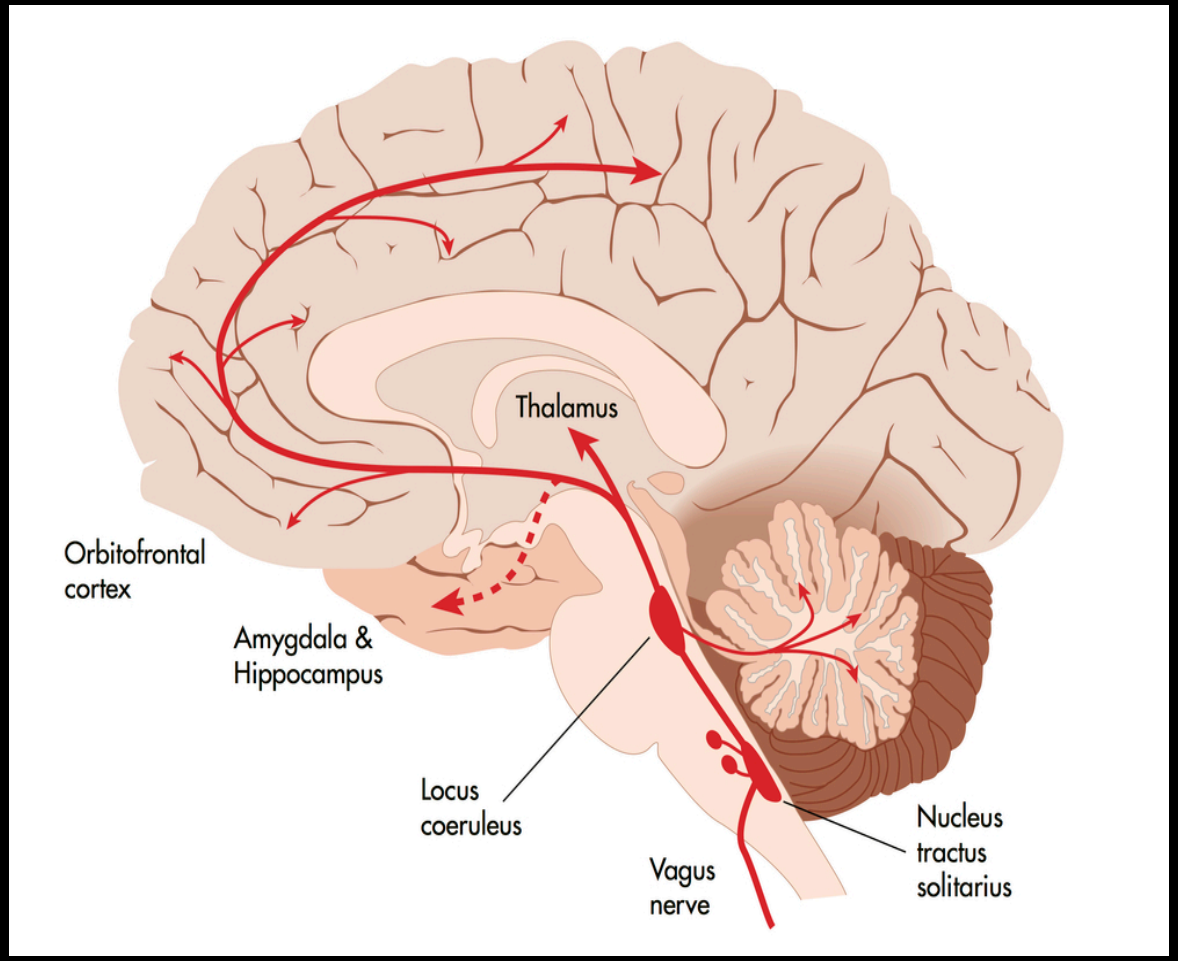
- Narrowing of the arteries
- Vagus nerve neck surgery
- Significant changes in blood pressure or heart rate
- Certain medical conditions involving the head

gammaCore should not be used by people with:

- Certain implanted medical devices, such as a pacemaker or hearing aid implant
- A metallic implant at or near the neck such as a stent, bone plate or screw
- Additionally, gammaCore should not be used at the same time as another electronic device such as a TENS unit or a mobile phone.

vVNS: Pathophysiology

- Gammacore activates the Vagus nerve with gentle electrical stimulation blocks pain signals
- Vagal nerve stimulation may modify cortical excitability through projections from nucleus tractus solitarius to the locus coeruleus, raphe nucleus, then to subcortical/cortical regions
- May inhibit Trigeminal complex activation and glutamate release



Clinical Evidence: nVNS (Gammacore)

	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy	Safet
nVNS CM Prevention	RCT x 2 months, open label x 6 months	2, 120 second stimulations, 3x day for 2 months	RCT=59 OL=27	Baseline mean headache frequency 21.5 days /month Primary endpoint met: sage and tolerable Exploratory endpoints RCT1.4 reduced headache days/month vs 0.02 for sham (P-0.56) OL 4 reduced headache days/month	Well tolerated AEs reported: upper respiratory track infections, gastrointestinal symptoms
nVNS Acute Treatment of migraine PRESTO study	RCT	Bilateral 120 second stimulations within 20 minutes of migraine onset; allowed to repeat once after 15 minutes if pain not improved	248	Study failed to meet its primary end point of pain free at 120 minutes (P=0.067) but met several secondary endpoints including pain free at 30 minutes, (P=0.023) and pain relief at 120 minutes (P=0.004)	Application site discomfort (2.5%) Nasopharyngitis (1.6.5)
CLUSTER Studies PREVA ACT1 ACT2	Chronic /episodic		97(CCH) 133 (85 ECH, 48)		Headache (8%) Dizziness (6%) Throat pain (6%) Neck pain (6%) Lip or facial twitching (11%) Parenthesis (4%)

sTMS

- Adult and Adolescent (12-17)
- Prevention: 4 pulses bid
- Acute: 3 pulses up to 3 times per attack
- Migraine with aura
  - 2 pulses at aura onset

sTMS: Side effects and Contraindications

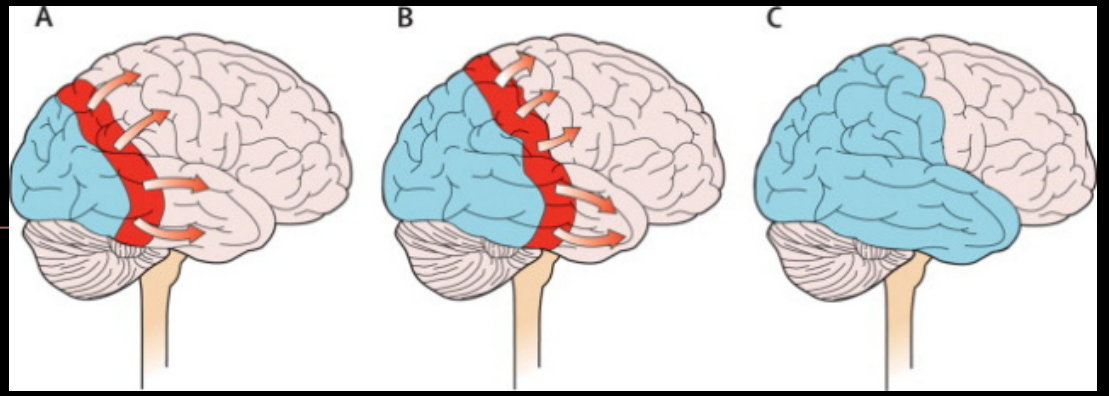
- Most common Side effects:
  - lightheadedness
  - tingling
  - tinnitus

- Do not use the System
  - cardiac pacemaker, vagus stimulator (VNS) or other implanted neurostimulator, implanted cardioverter defibrillator (ICD) or any implanted medical.
  - Other metal items: metal fragments, bullets, and tattoos with metallic ink.
  - Epilepsy, head injury, stroke
  - Near or in water.
- Warning
  - Keep metal coins credit cards 2 ft from device
- Dental implants, fillings or other dental appliances are okay and are not affected by the device. *

Pregnancy - sTMS

- Dodick et al. 2010
  - Repetitive TMS use during pregnancy had been described in 2 cases reports no adverse event were reported for either mother or baby
  - The committee on Possible Effects of electromagnetic Fields on Biologic systems(committee of the National Research Council)reviewed exposures to electrical and magnetic fields and concluded that reproduction and development in animals have not beenshown to be affected by exposure to low frequency electric and magnetic fields
  - sTMS delivers a peak field of less than 1 Gauss Treatment exposure for a full term pregnant uterus for 2/1000 a second pre treatment.
- Bhola et al 2015
  - RCT of sTMS for migraines with and without aura (n=190) 3 were pregnant and received TMS in the 2nd trimester. All 3 treated throughout pregnancy and reported benefit. All 3 had no complications at birth.
- Kim et al. 2019
  - RCT rTMS in pregnant women with depression. 22 depressed pregnant all in 2nd/3rd trimester, 20 sessions the right prefontal cortex. Late preterm birth (PTB) occurred in 3 women receiving active TMS. All other maternal and delivery outcomes were normal.

Transmagnetic Stimulation



- Technology used > 30 yrs (depression, epilepsy, and movement disorders)
- TMS creates an Ionic current to underlying cortex
- Proven to change the firing pattern and excitability of the cortical neurons with effect dependent on the frequency of simulation
- Single pulse–depolarize neurons and multiple can modify plasticity of the cortex creating an inhibitory effect on cortical excitability low frequency and excitatory effect with high frequency.
- Based on hypothesis effect could disrupt aura cortical spreading depression modulate the cortico-thalamic circuits by which CSD is thought to induce central pain.

Clinical Evidence: sTMS

Study	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy	Safety
sTMS Migraine prevention ESPOUSE study	Open Label prospective Observational	4 pulses twice daily as prevention and additional 3 pulses, up to 3 times per attack	132	Baseline Headache days 9.06/m Baseline acute medication use 5.24 days/m 2.75 reduced hdm @ month3* 50 % responder rate: 46%* 2.93 reduced MUM at month 3	Well tolerated Common AEs: tingling, and tinnitus
sTMS Acute treatment of migraine with Aura	RCT	2 pulses at aura onset	164	Pain Free at 2 hours with sTMS vs Sham (P=0.0179	Headache (2%) Migraine (2%) Sinusitis (2%)
sTMS for Migraine Prevention in Adolescents (12-17)	Open Label Study	4 pulses twice daily as prevention and additional 3 pulses, up to 3 times per attack	21	Feasible, well tolerated and acceptable Final weeks trail measured: 2.5 reduction in headache days (P=0.36) 36 point reduction of PedMidas score(P=0.26)	(1)Tingling sensation at delivery site (1)Poor tolerance of noise device made (1)Worsened headache

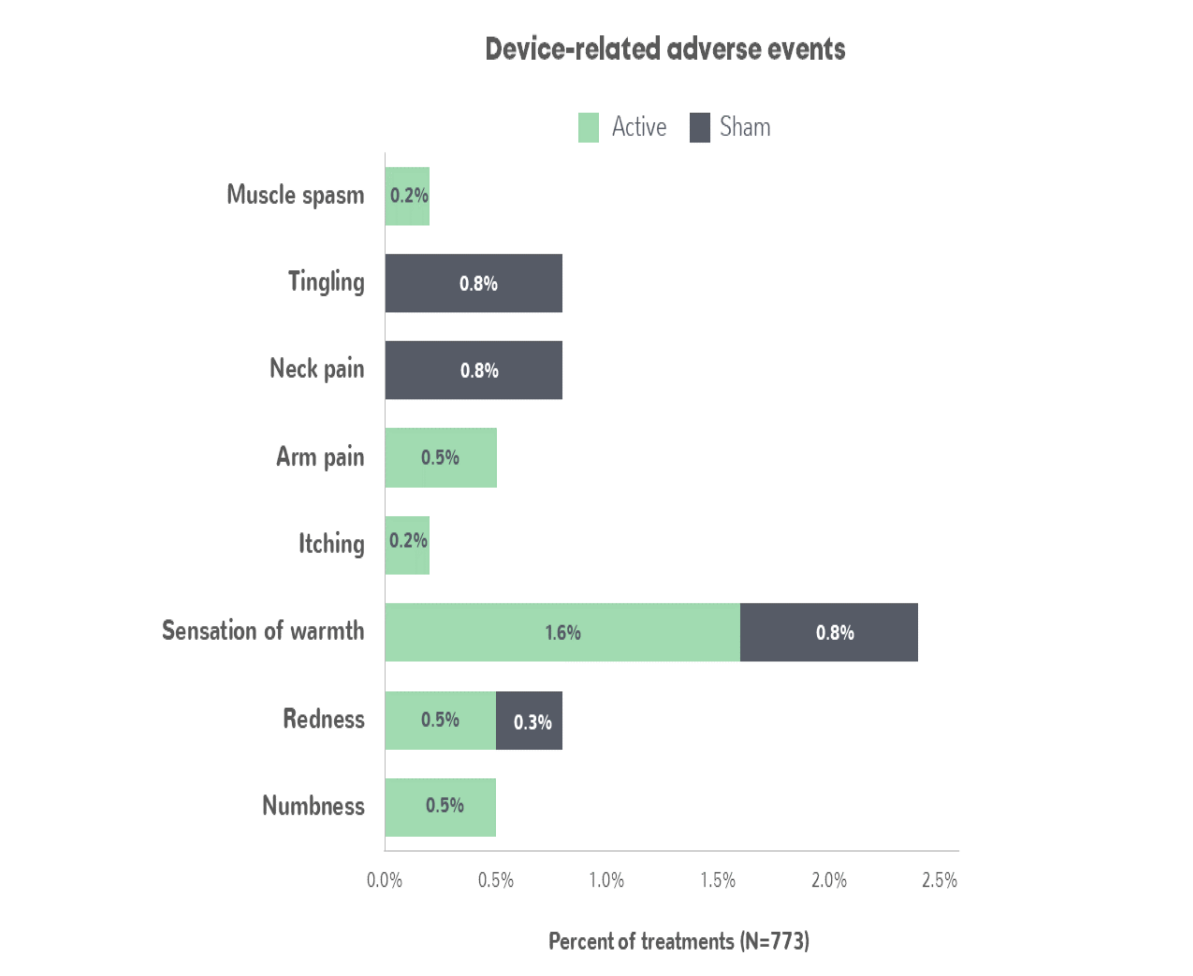
REN (Nerivio)

- For Acute migraine attacks only
- Indicated for episodic migraine

- Start onset of the migraine (within 60 minutes of aura or onset of migraine pain)

- Intensity level strong but not painful
- Continue treatment for 45 minutes
- May continue with activities

REN: Side effects and Contraindications

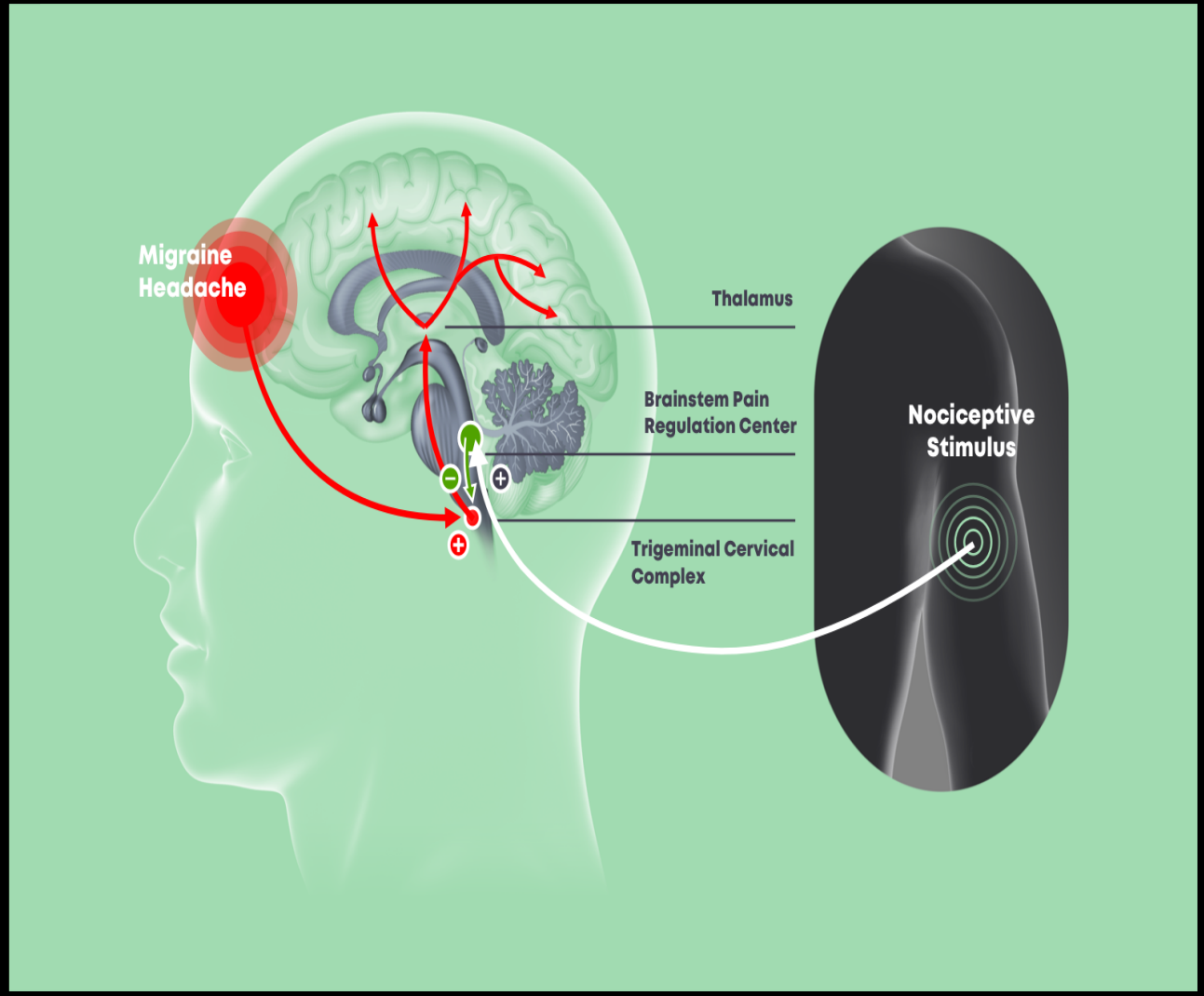


- Should not be used
  - with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.
  - uncontrolled epilepsy
  - active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device.

- Precautions:
  - Do not use the device on an arm with a metallic implant.
  - Do not use the device simultaneously with another electrical stimulation device
  - Do not use the device while driving, cycling, or operating any vehicle or machinery
  - Do not use the device on wet skin or when bathing, showering, during exercise, while sweating or in high humidity
  - Do not use the device in the presence of electronic monitoring equipment (e.g., cardiac monitors, ECG alarms)
  - Do not use the device in a magnetic resonance imaging (MRI) environment

REN (Nerivio): Pathophysiology

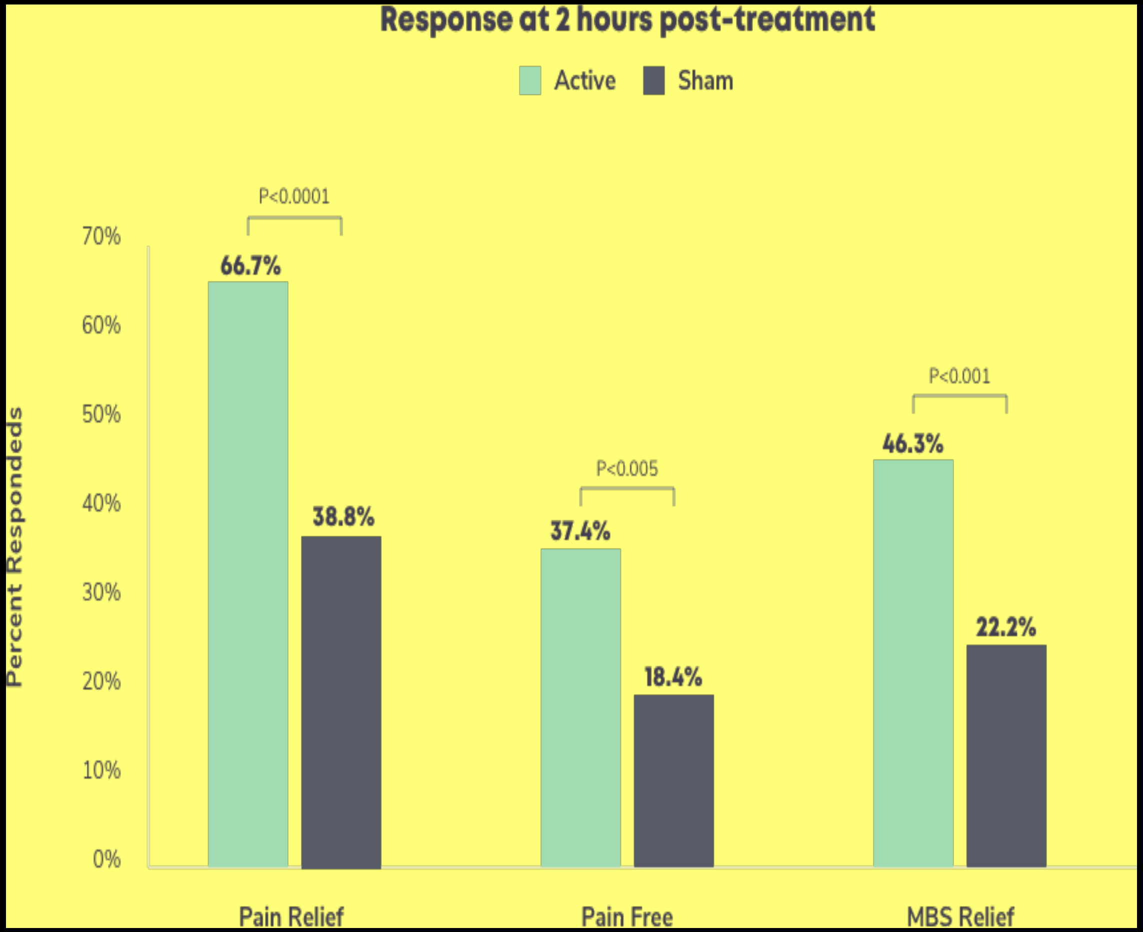
- Stimulates C and A alfa nociceptive sensory fibers of the upper arm above depolarization thresholds but below perceived pain threshold.
- Noxious info reaches the brain stem through the ascending pathway. This info activates the descending pain inhibitory pathway involving the brain stem pain regulation center (which includes the PAG, RVM, and sub-neucleus reticularis dorsalis (SDRI) and the release of serotonin and noradrenalin, which inhibit incoming messages of pain in the trigeminal cervical complex (TCC) that occur during migraine attack.

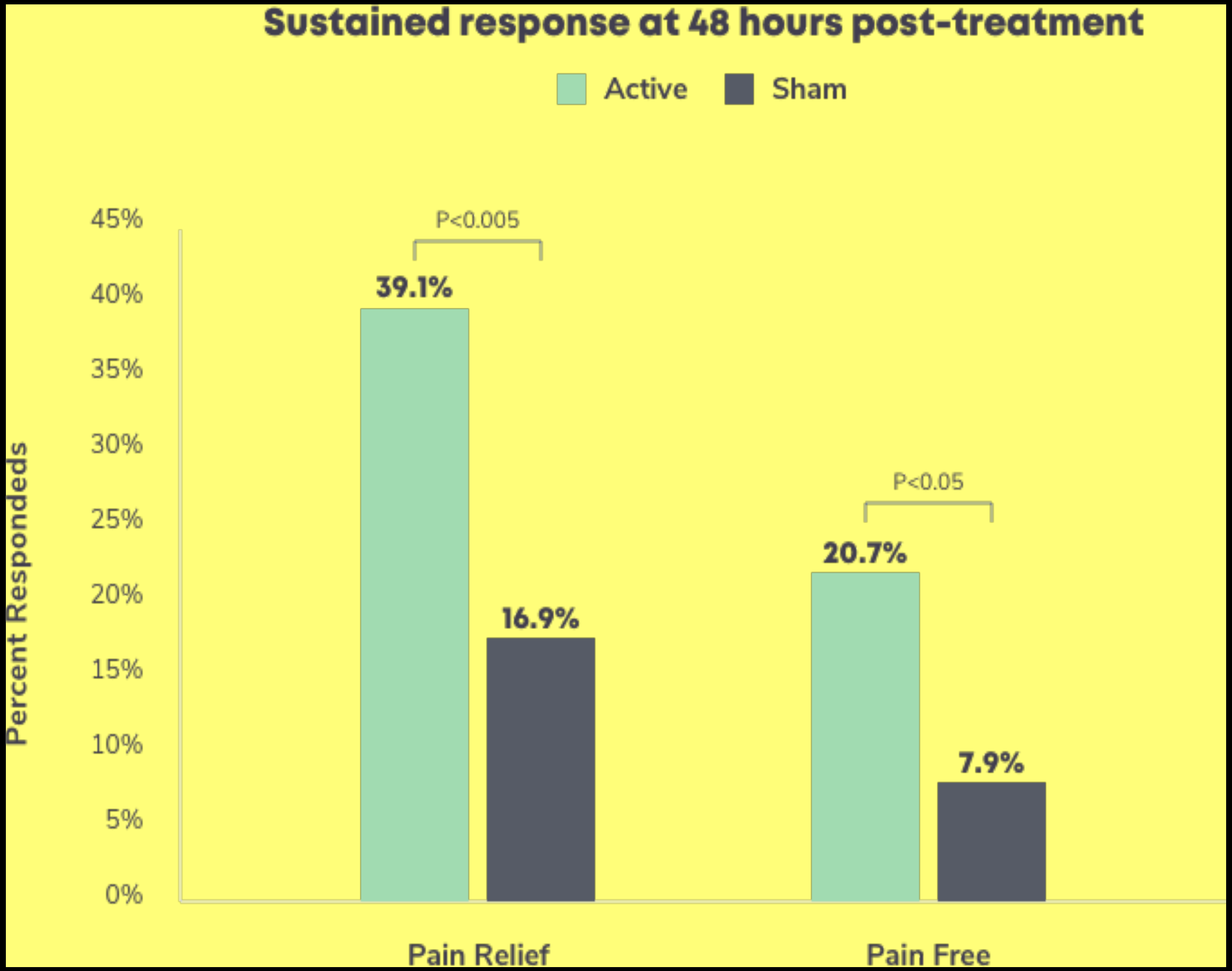


REN (Nerivio) Clinical Trials

- Pilot study – single center crossover sham controlled
  - 86 participants 71 treated with migraine with or without aura
  - 2-8 attacks /month without preventive medication
  - Random 1-4 different treatments
  - 64% pain reduction > 50% treated group
  - 26% pain reduction in sham group
- Pivotal Study RCT (sham) multi center
  - 296 252 randomized active treatment (n=126) sham treatment (n=126)
  - 2-8 attacks < 12 headache days a month
  - Either no or stable prevention medication

Clinical Evidence: REN (Nerivio)





Patient Selection: Special Considerations

- Does not like to take medications
- Sensitive to medications
- Use for adolescents
- Medication Overuse – treatment option that can avoid medication use
- Pregnancy*

Barriers

PAINWEEK®

Summary

- Migraine is a Brain Disorder
- Goal – Migraine Freedom
- Make the right diagnosis with a comprehensive plan
- Neuromodulation for Migraine Management is an Excellent option for both prevention and acute migraine attacks
- Advocate for better access and coverage

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