NEXT GENERATION
MIGRAINE THERAPIES
AMERICAN HEADACHE SOCIETY

Procedures and Neuromodulatory Approaches in Migraine

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AMERICAN HEADACHE SOCIETY
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Disclosure: Dr. Rashmi B. Halker Singh MD FAHS

Advisory Board: Teva, Impel, Supernus

Learning Objectives

Review ambulatory procedures for headache.

Differentiate the neuromodulatory approaches in migraine.

Ambulatory procedures for headache

Procedure	Disorders	Efficacy	Safety concerns
Peripheral nerve blocks			
Trigger point injections			
OnabotulinumtoxinA			

Rationale for nerve blocks in headache

- Treatment latency of older preventive treatments
- Patients intolerant/partially responsive to medication
- Limit frequent/excessive use of acute medications

Medical contraindications for specific treatments

- Pregnancy and lactation
- Elderly
- Polypharmacy

Coexistent neck pain and tender trigger points

- Immediate relief from headache and associated symptoms
- Generally safe, relatively easy to perform
- Evidence strong for cluster headache and migraine

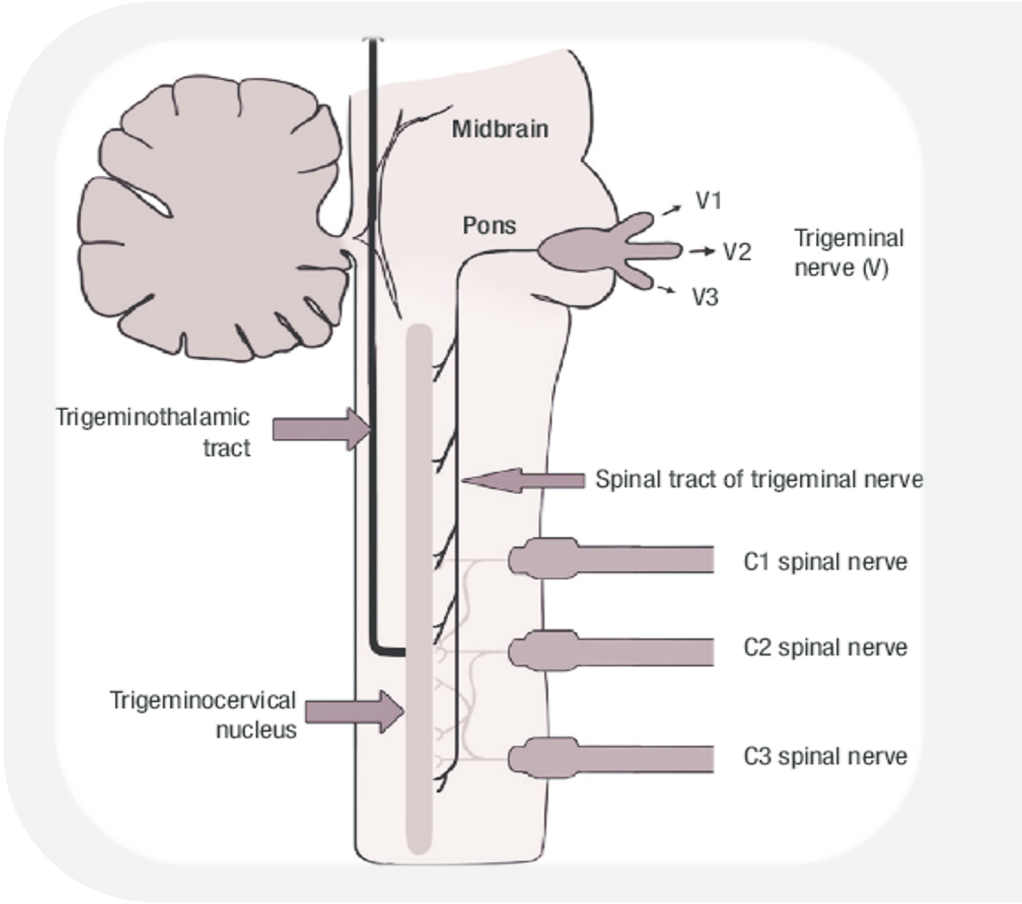
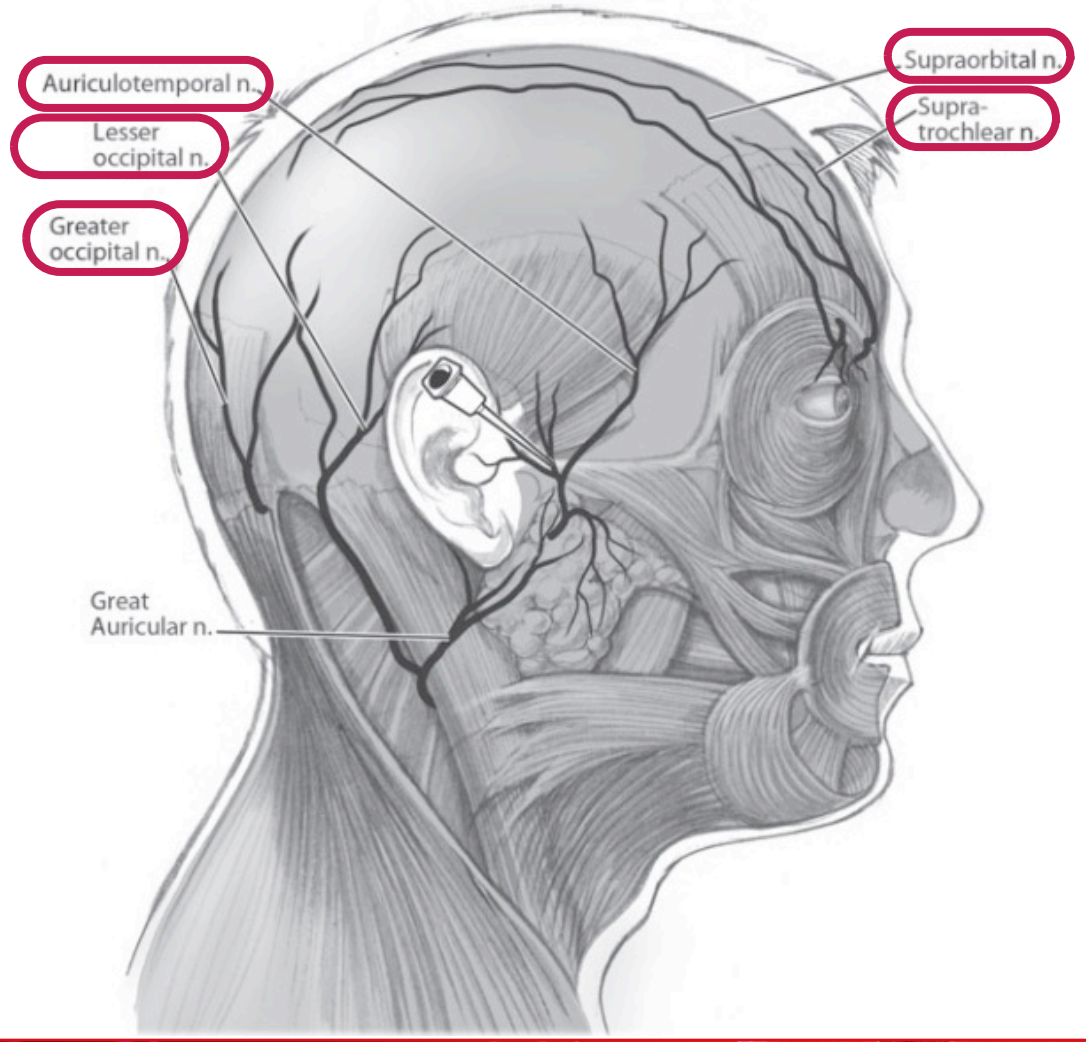


Image source: Choi I, Jeon SR. *J Korean Med Sci*. 2016;31:479–488.

Peripheral nerve blocks



Blumenfeld A et al. *Headache*. 2013;53:437–446.

Local anesthetics for migraine

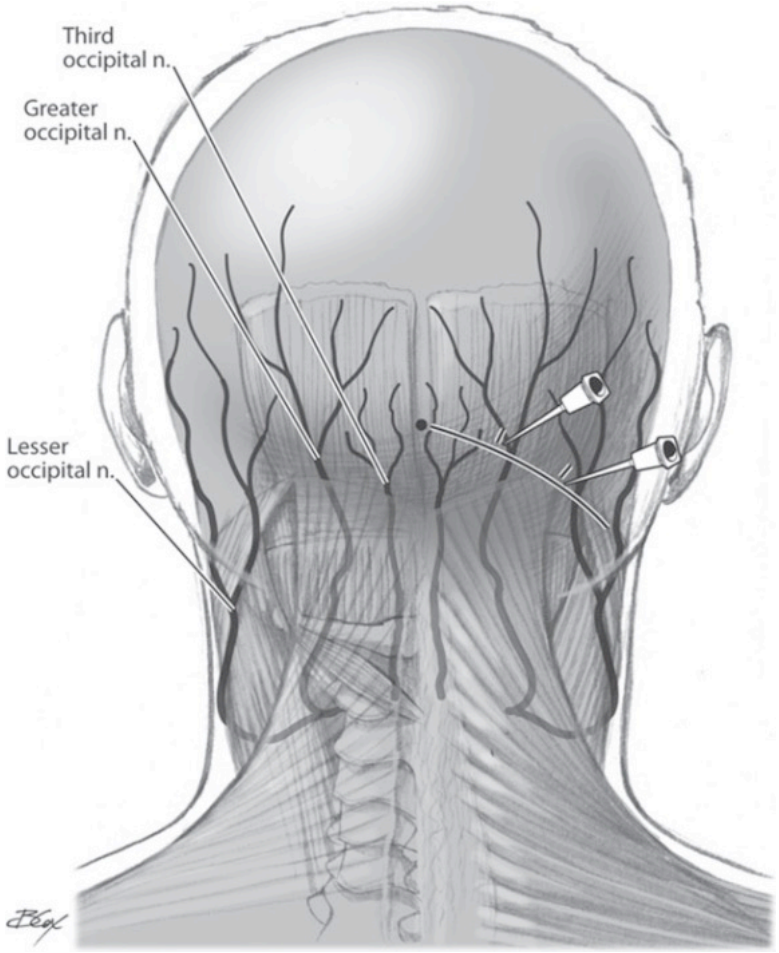
- Duration of nerve blockade depends on dose and pharmacokinetic properties of local anesthetic
- Longer than expected duration of analgesic (vs anesthetic) effect of nerve block is common
- Mechanism of prolonged analgesic effect incompletely understood

	Lidocaine	Bupivacaine	Ropivacaine
Typical concentration	1–2% (10–20 mg/mL)	0.25–0.5% (2.5–5 mg/mL)	0.2–0.5% (2–5 mg/mL)
Duration of effect*	1–3 hours	4–8 hours	4–9 hours

Adding steroid to greater occipital nerve injection recommended for cluster headache only

*Subcutaneous injection.

Greater occipital nerve block technique



- Identify nerve at scalp entry
  - Superior nuchal line
  - ⅓ distance between occipital protuberance and mastoid process
- 25–30-gauge needle inserted subcutaneously
- Inject 1–4 mL at each site

Blumenfeld A et al. *Headache*. 2013;53:437–446.

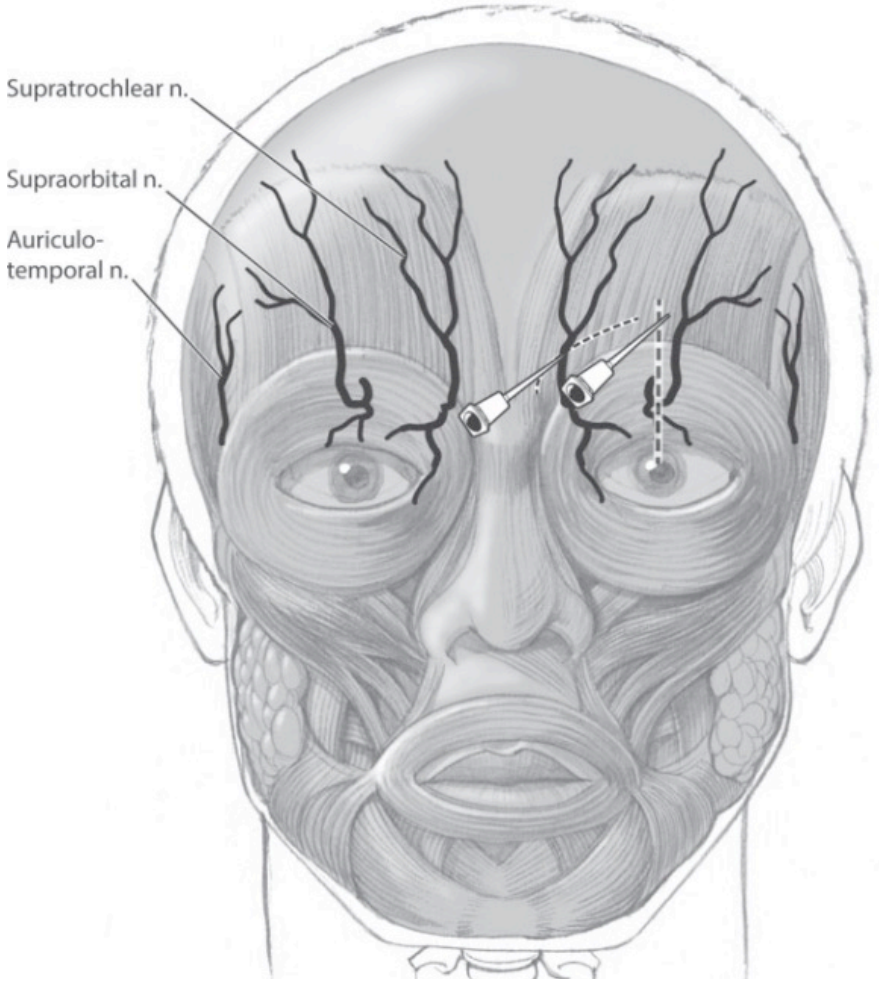
Supratrochlear and supraorbital nerve block technique

Supratrochlear

- Use 30-gauge needle
- Inject 0.2–1 mL superomedial corner of orbit—at or just above eyebrow

Supraorbital

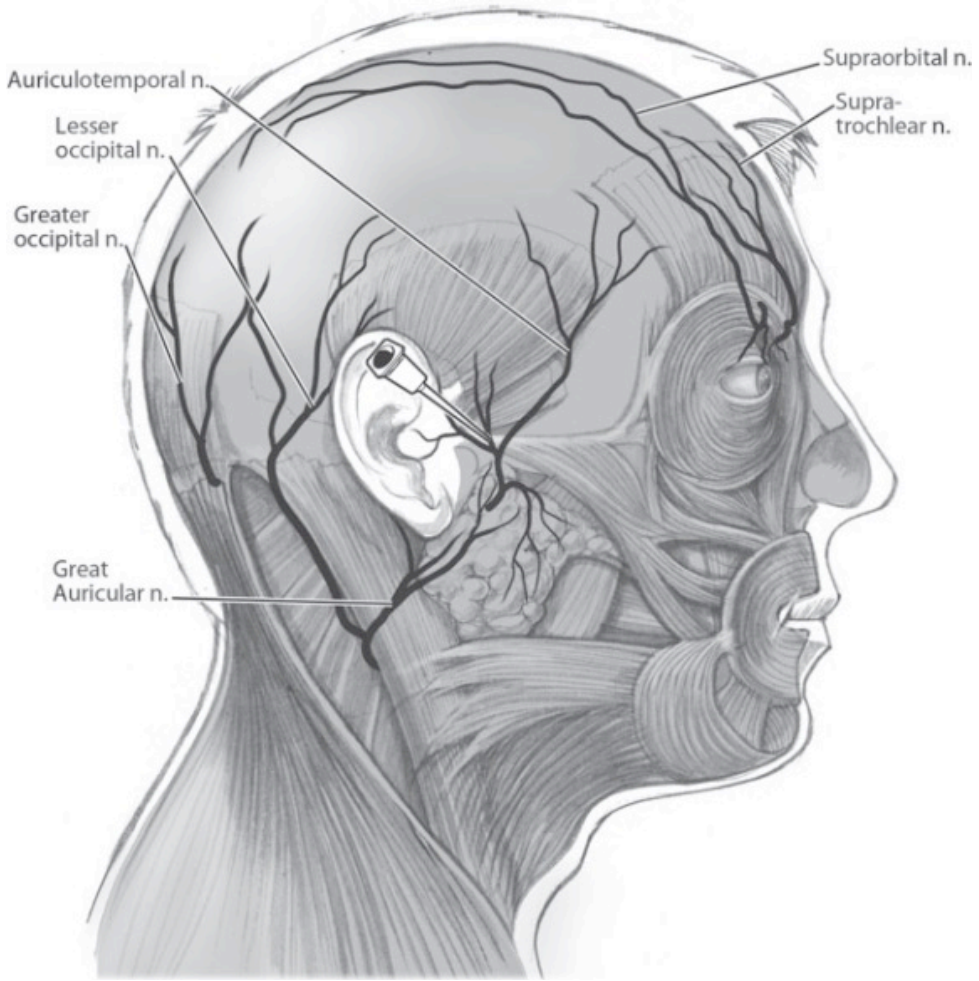
- Redirect needle 2 cm laterally
- Inject 0.2–1 mL
- Alternative: inject at or just above eyebrow, on midpupillary line



Blumenfeld A et al. *Headache*. 2013;53:437–446.

Auriculotemporal nerve block technique

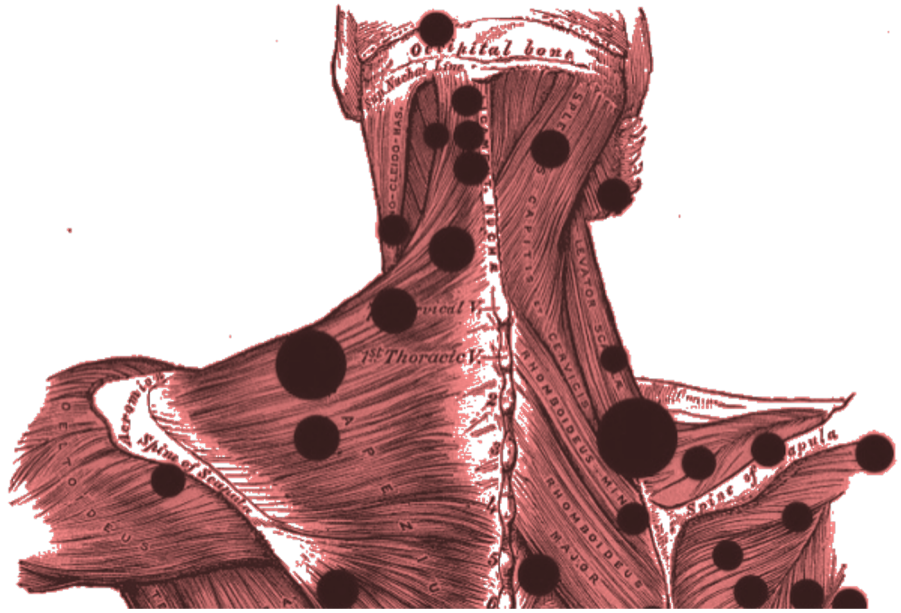
- Inject 0.5–1 mL 2 mm anterior to temporal artery at a depth of 4–6 mm
- Additional 0.25 mL injections may be performed more superiorly, at the temporal fossa
- Alternative: inject at the posterior margin of the mandibular ramus, just inferior to the tragus, at a depth of 20 mm



Blumenfeld A et al. *Headache*. 2013;53:437–446.

Myofascial pain syndrome

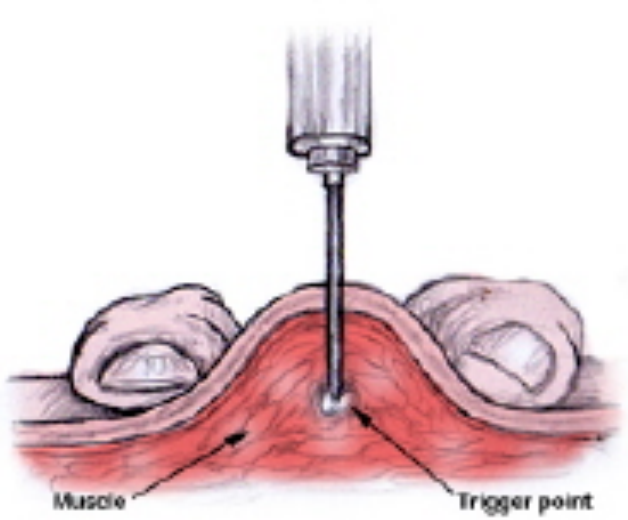
- Tender, taut band, twitch
- Refers pain to region corresponding to pain problem
- Existence/reliable identification may be difficult to establish
- Active trigger points
  - Found more often in patients with episodic tension-type headache and migraine
  - Associated with greater attack frequency, duration, and severity



Simons DG et al. *Myofascial Pain and Dysfunction: The Trigger Point Manual, Vol. 1 – Upper Half of Body*. London: Williams and Wilkins; 1999. Fernández-de-Las-Peñas C et al. *Headache.* 2006;46:1264–1272. Calandre EP et al. *Eur J Neurol.* 2006;13:244–249. Robbins MS et al. *Headache.* 2014;54:1441–1459.

Trigger point injection technique

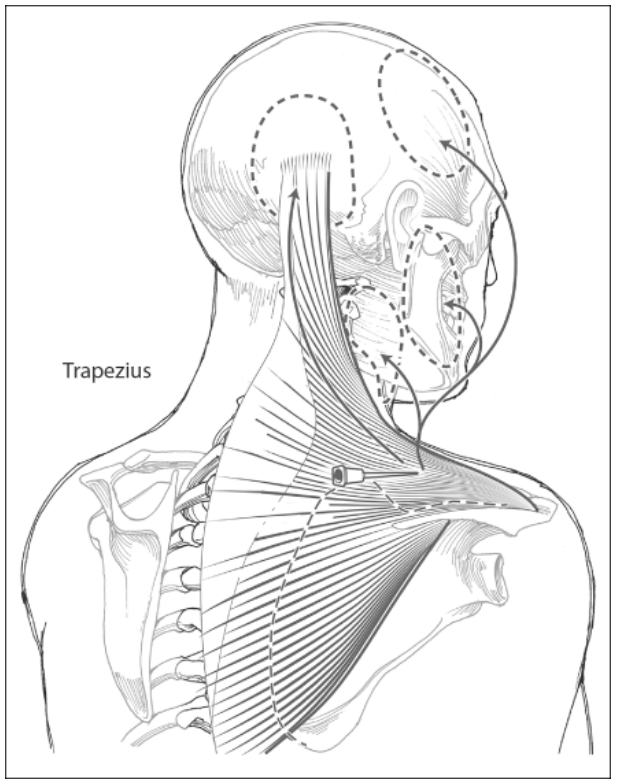
- Seated or recumbent position
- 25–30-gauge, 1.5-inch needle
- Hold overlying skin and stabilize between thumb and index finger
- Insert 1–1.5 cm away from the trigger point, advance at 30°
- Local anesthetics
  - 0.1–0.3 cc of 1% lidocaine, 0.5% bupivacaine, or 0.5% ropivacaine
  - 1–4 mL per site



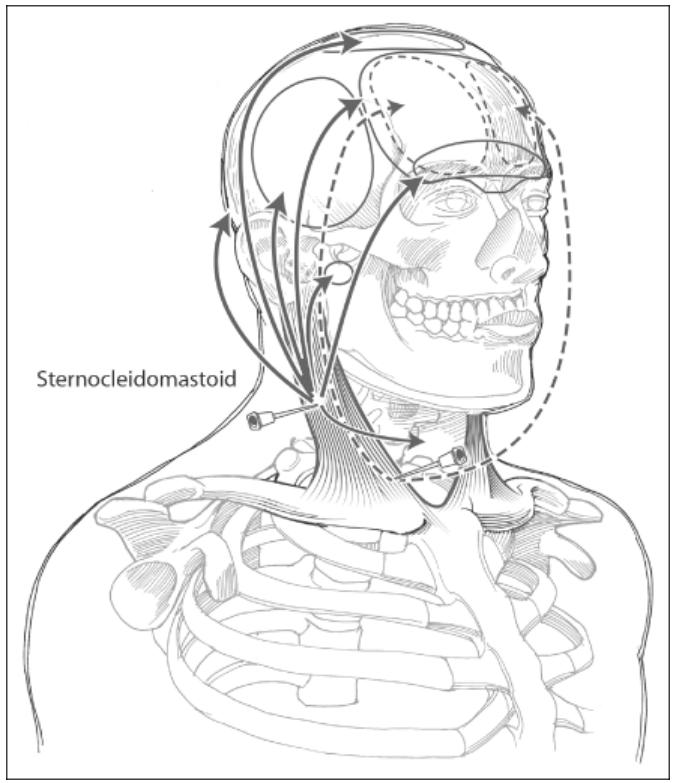
Robbins MS et al. *Headache*. 2014;54:1441–1459.

Trigger point injections: three most common muscles

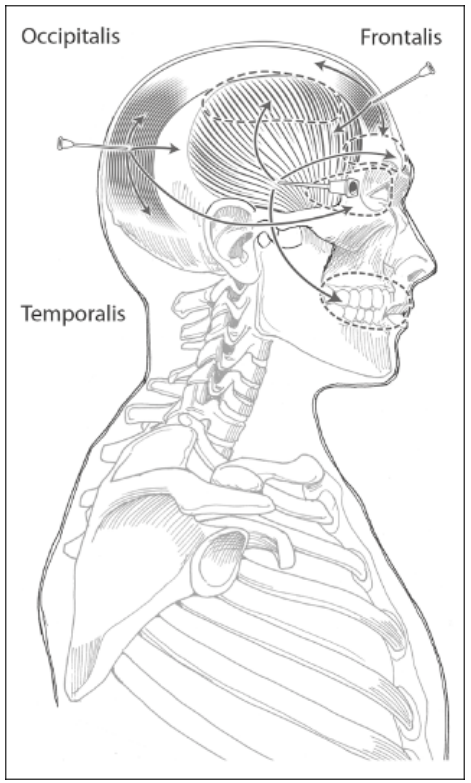
Trapezius



Sternocleidomastoid



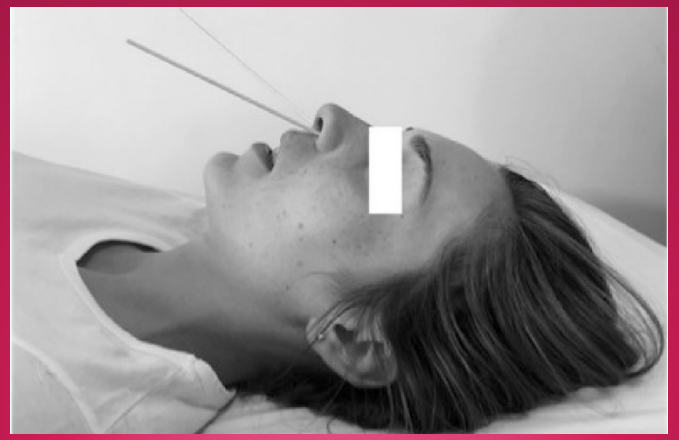
Temporalis



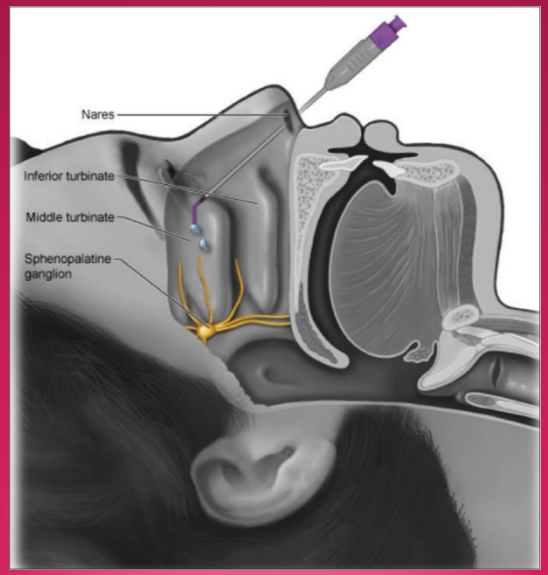
Robbins MS et al. *Headache*. 2014;54:1441–1459.

Sphenopalatine ganglion blocks

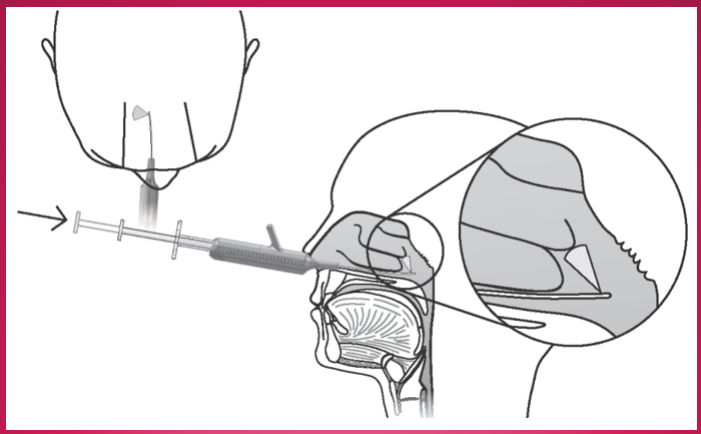
Traditional procedure for SPG blockade in supine position with a cotton-tipped applicator soaked in anesthetic solution[1,2]



Sphenocath® catheter insertion along the anterior nasal passage and placement superior to the middle nasal turbinate[3]



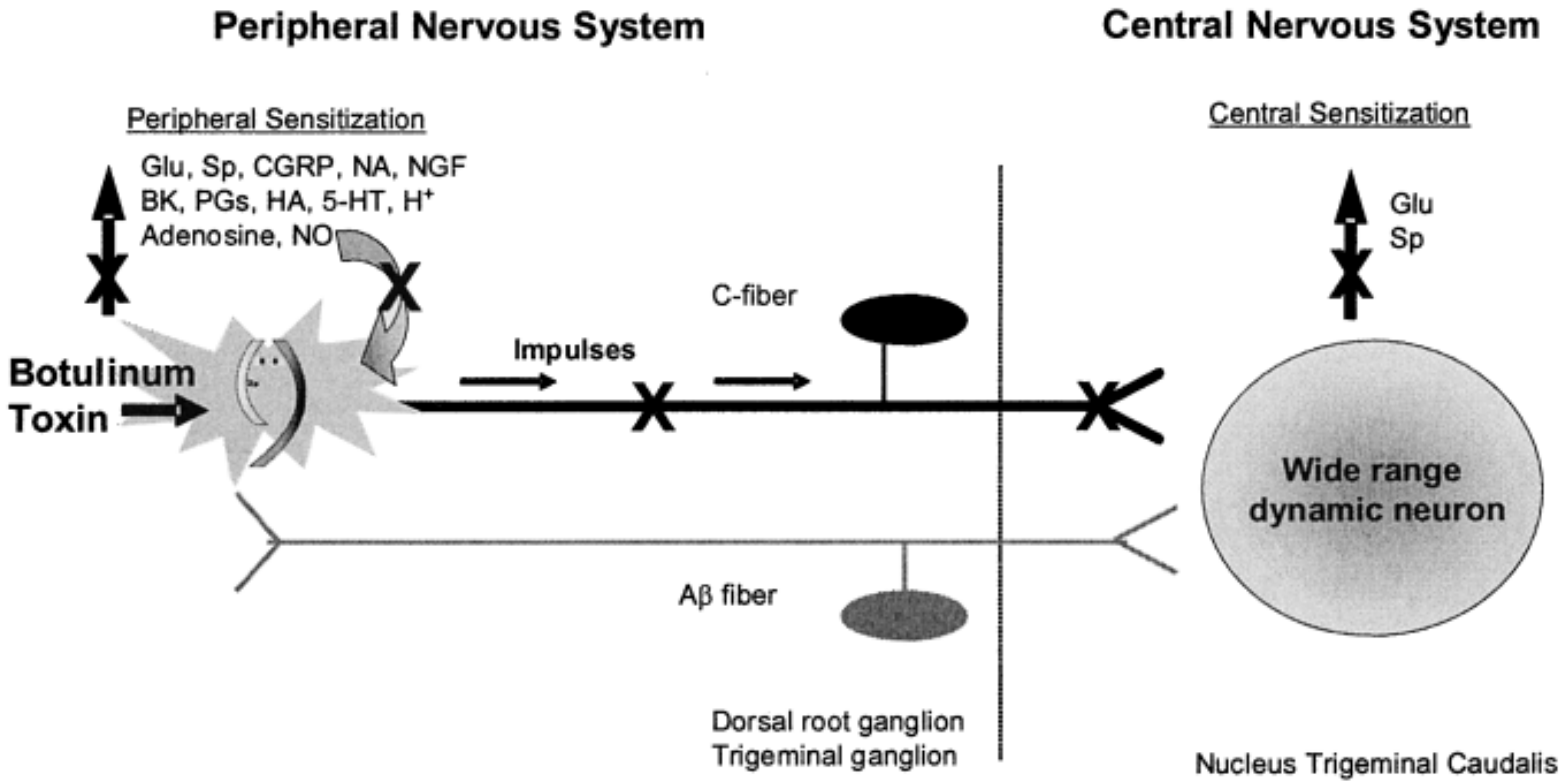
Tx360® nasal applicator insertion and placement in inferior aspect of nasal cavity and catheter tip destination below middle nasal turbinate[1]



SPG, sphenopalatine ganglion.

1. Robbins MS et al. *Headache.* 2016;56:240–258. 2. Furtado I et al. *Rev Bras Anestesiol.* 2018;68:421–424. 3. Forrest A et al. *Am J Interv Radiol.* 2018;2:1–4.

OnabotulinumtoxinA in migraine: works on more than muscle



Reduces peripheral sensitization:

Inhibits release of several neuronal signaling markers

Reduces central sensitization:

Reduces c-*fos* gene expression in dorsal horn, trigeminal nucleus caudalis

Aoki KR. *Headache.* 2003;43(Suppl 1):S9–15. Kosaras B et al. *J Comp Neurol.* 2009;515:331–348. Schueler M et al. *Pain.* 2013;154:1622–1631. Burstein R et al. *Cephalalgia.* 2014;34:853–869.

OnabotulinumtoxinA injection technique considerations

NEEDLE SIZE

30-gauge with 1 cc tuberculin syringe

PATIENT POSITION

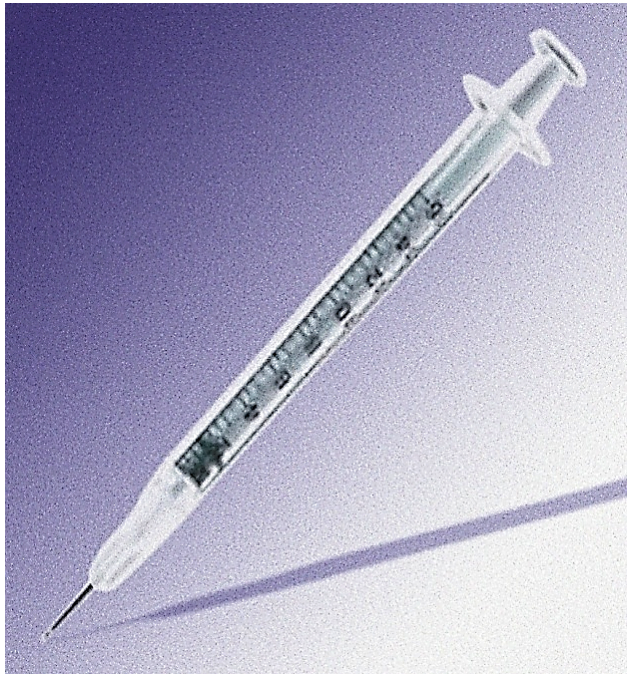
Sitting for posterior injections

Lying for frontal and temporalis injections

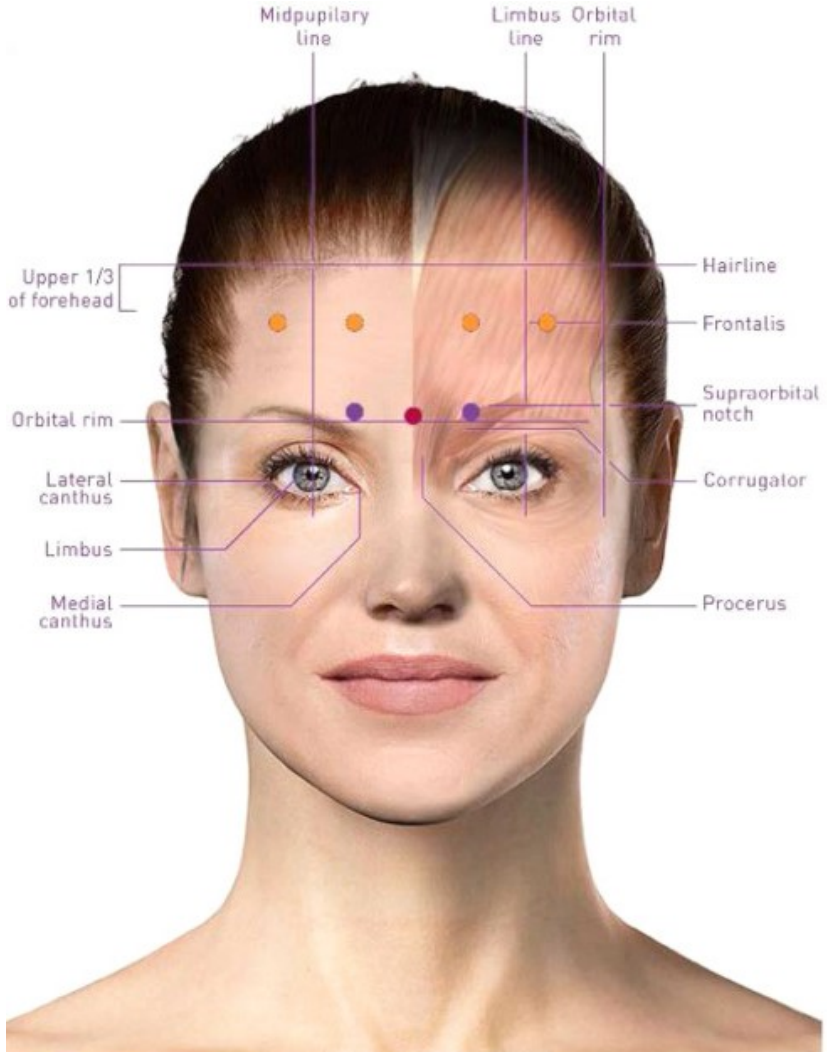
DILUTION

100 unit (2 mL normal saline)

200 unit (4 mL normal saline)



Fixed-site, fixed-dose injection-site locations



- Corrugator
  - 5 Units (0.1 mL) in each site
  - Total of 10 Units divided into 2 sites
- Procerus
  - 5 Units (0.1 mL) in 1 site
  - Total of 5 Units
- Frontalis
  - 5 Units (0.1 mL) in each site
  - Total of 20 Units divided into 4 sites

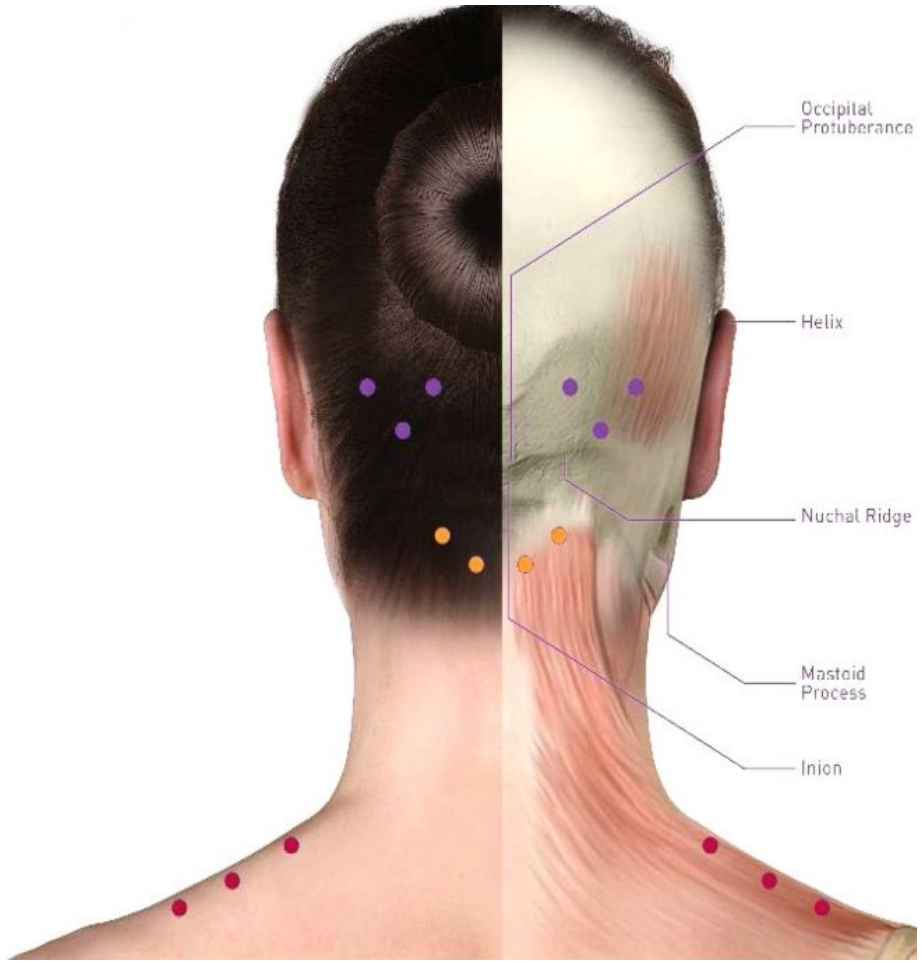
Blumenfeld AM et al. *Headache*. 2017;57:766–777.

Fixed-site, fixed-dose injection-site locations

- Temporalis
  - 5 Units (0.1 mL) in each site
  - Total of 40 Units divided into 8 sites

Blumenfeld AM et al. *Headache*. 2017;57:766–777.

Fixed-site, fixed-dose injection-site locations



- Occipitalis
  - 5 Units (0.1 mL) in each site
  - Total of 30 Units divided into 6 sites
- Trapezius
  - 5 Units (0.1 mL) in each site
  - Total of 30 Units divided into 6 sites
- Cervical paraspinal
  - 5 Units (0.1 mL) in each site
  - Total of 20 Units divided into 4 sites

TOTAL DOSE
155 Units divided between 31 sites

Blumenfeld AM et al. *Headache*. 2017;57:766–777.

Procedures Summary

- Injections for headache can be performed effectively, safely, and efficiently after gaining a basic understanding of the indications and anatomic landmarks
- Peripheral nerve blocks are useful for many headache disorders
- Trigger point injections are identified by physical examination and should be restricted to local anesthetics only
- OnabotulinumtoxinA is indicated for chronic migraine, and is effective, safe, and with few contraindications

Neuromodulatory approaches in migraine

FDA cleared

Non-Invasive

- Single-pulse transcranial magnetic stimulation (sTMS)
- External trigeminal neurostimulation (eTNS)
- Non-invasive vagus nerve stimulation (nVNS)
- Remote electrical neuromodulation (REN)

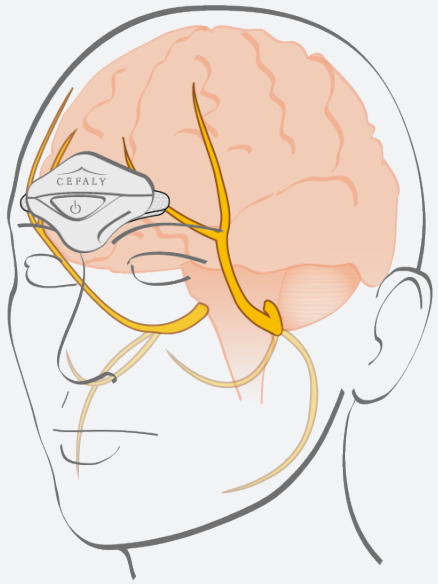
Invasive

- Occipital nerve stimulation
- Sphenopalatine ganglion stimulation

Best used exclusively in refractory patients who have failed previous treatments

Puledda F, Goadsby PJ. *Headache*. 2017;57:685–691.

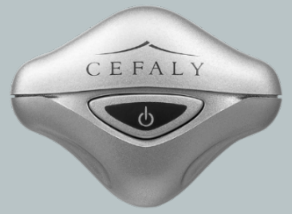
External trigeminal neurostimulation (eTNS)



Cefaly

- FDA cleared for both acute and preventive (in patients with three or more attacks per month) treatment of migraine
- Three **different** devices available, pre-programmed to deliver treatment sessions:

Cefaly Acute

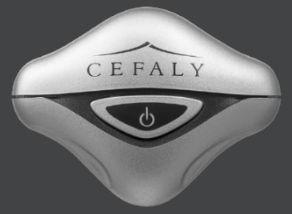


1-hour session with high impulse frequency, used during attack (preferably at beginning)

Cefaly Prevent

20-minute session used once daily (preferably in the evening)

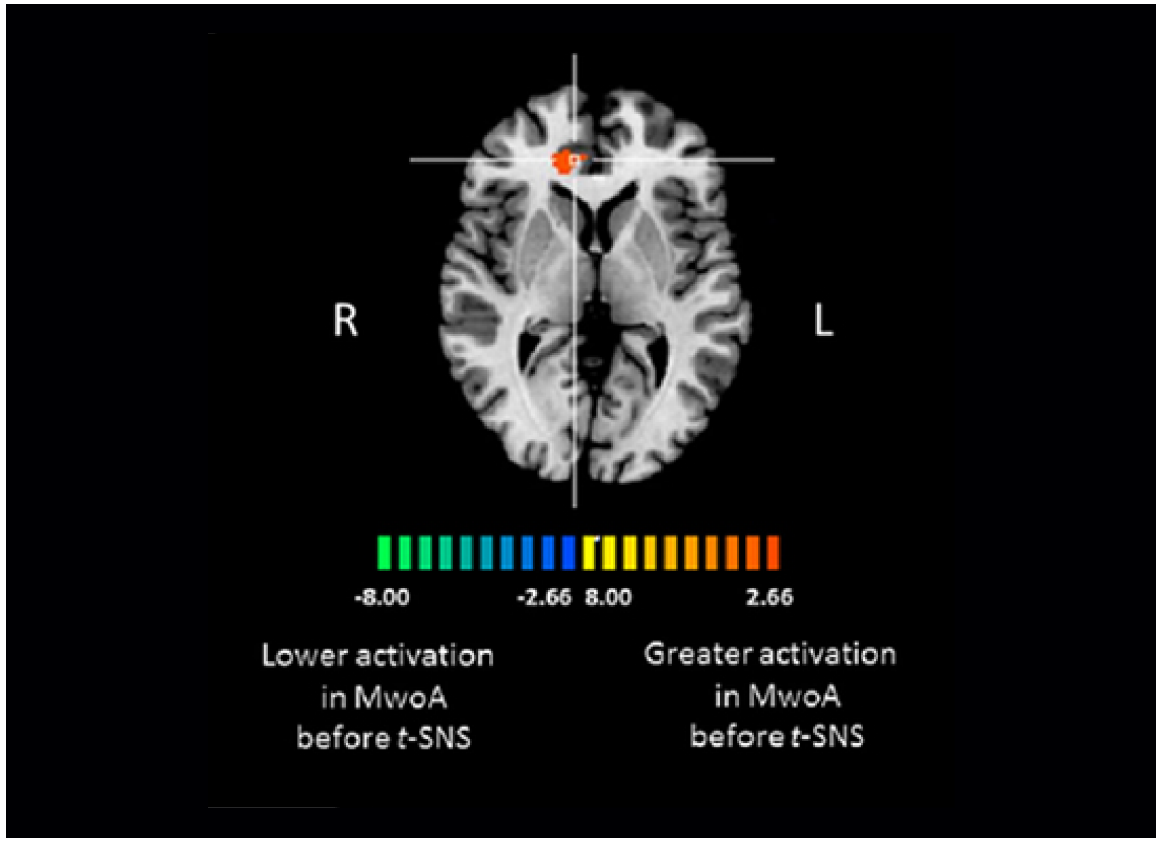
Cefaly Dual

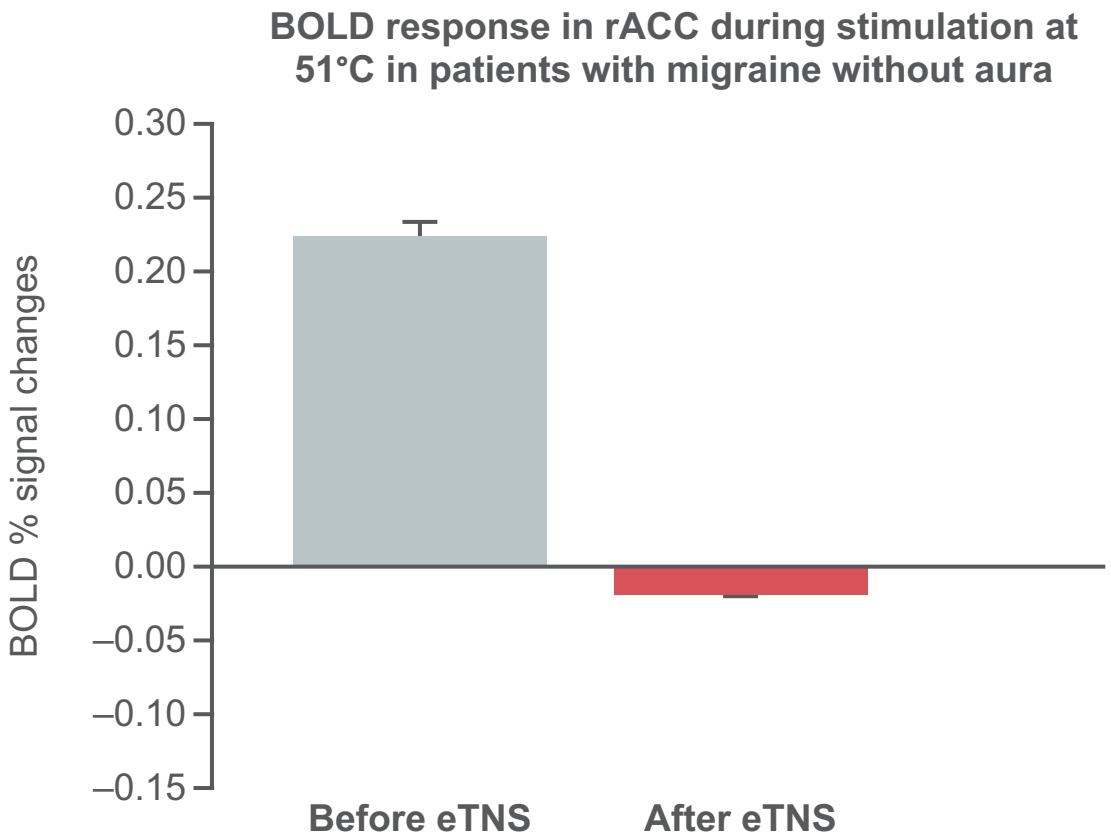


Both acute and preventive treatment settings

https://www.cefaly.us/en/how-to-use-it [accessed February 22, 2019].

Potential mechanism of action of eTNS



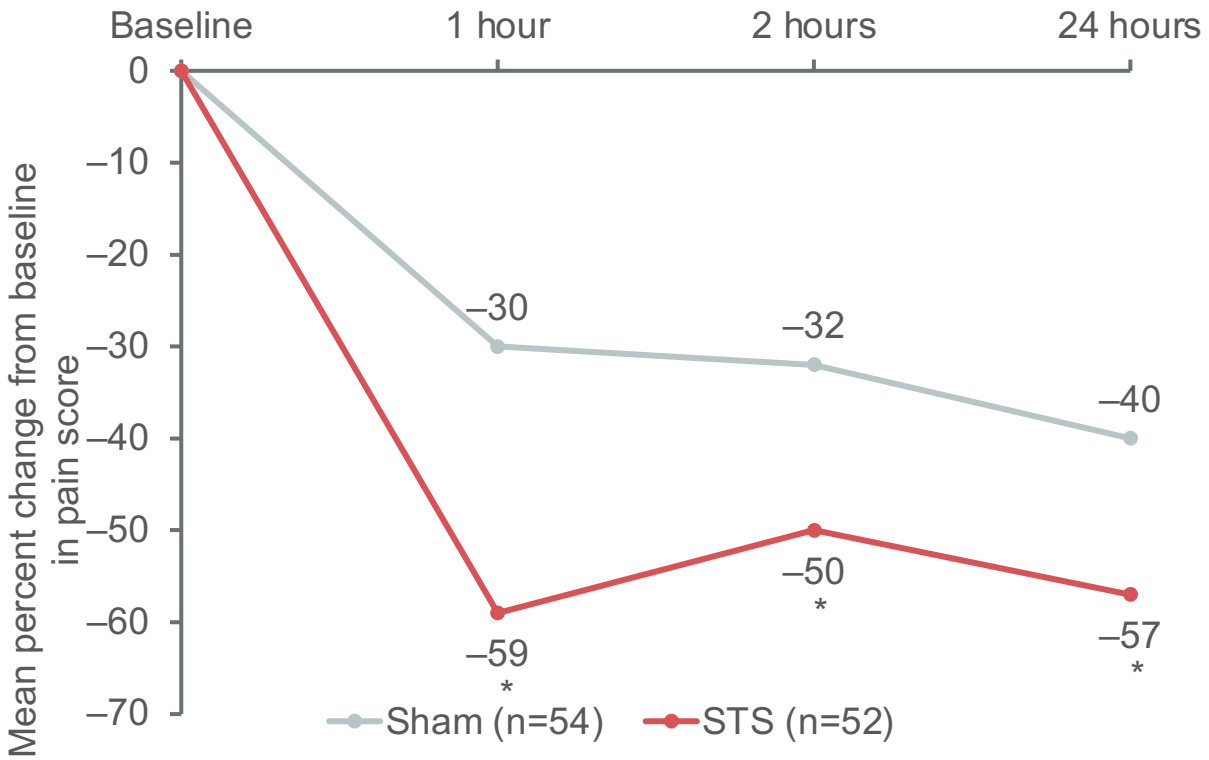


P<0.05 cluster level corrected.

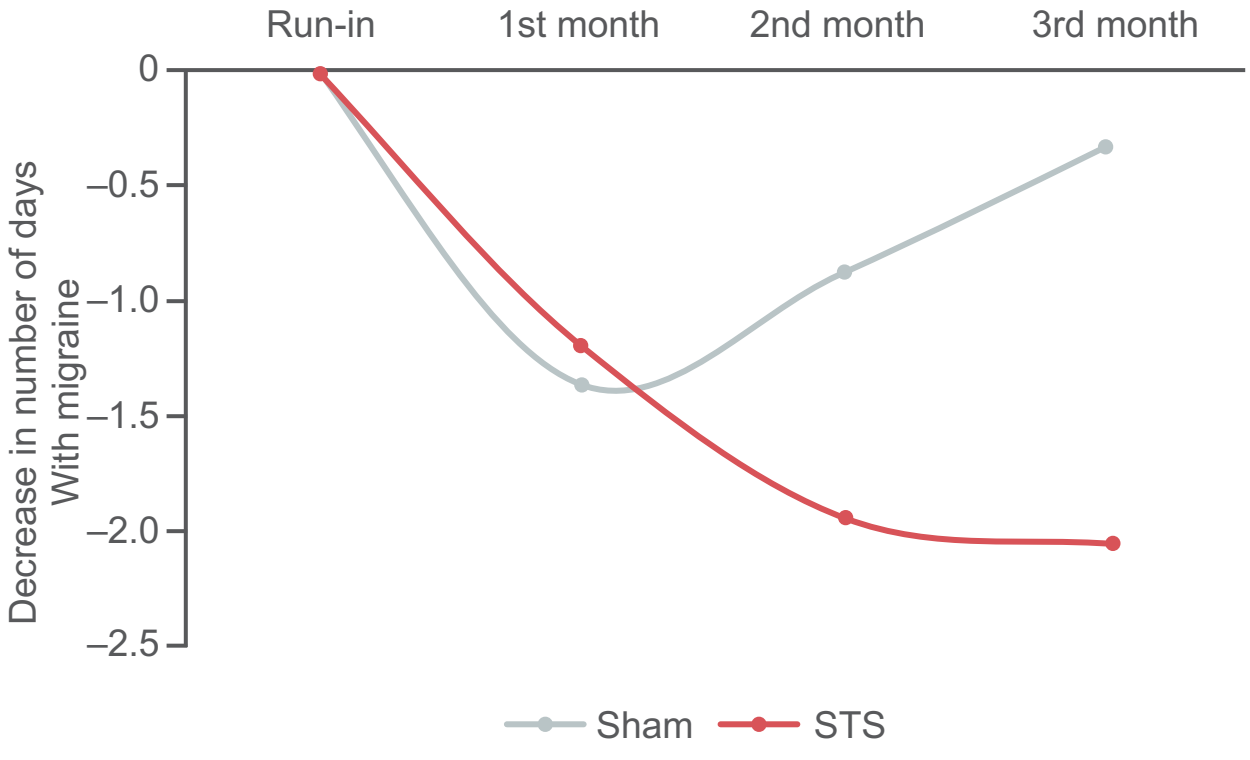
BOLD, blood oxygen level–dependent; rACC, right anterior cingulate cortex.
Russo A et al. *Front Neurol*. 2017;8:282.

Efficacy of eTNS for treatment of migraine

Acute[1]



Preventive[2]



*P<0.05 vs sham.

1. Chou DE et al. *Cephalalgia*. 2019;39:3–14. 2. Schoenen J et al. *Neurology*. 2013;80:697–704.

eTNS safety and patient satisfaction during device trial period

- 2313 patients tested eTNS devices for an average of 58 days
- 99 subjects (4.3%) reported AEs
- No serious AEs were reported
- The most frequent AEs were:
  - Local pain/intolerance to paresthesia (n=47; 2.03%)
  - Arousal changes (mostly sleepiness/fatigue, sometimes insomnia, n=19; 0.82%)
  - Headache after the stimulation (n=12; 0.52%)
- A transient local skin allergy was seen in two subjects (0.09%)

After the testing period, 47% of patients were not satisfied and returned the device

However, the compliance check showed that they used it on average only 49% of the recommended time

AE, adverse event.

Magis D et al. *J Headache Pain*. 2013;14:95.

Single-pulse transcranial magnetic stimulation (sTMS)

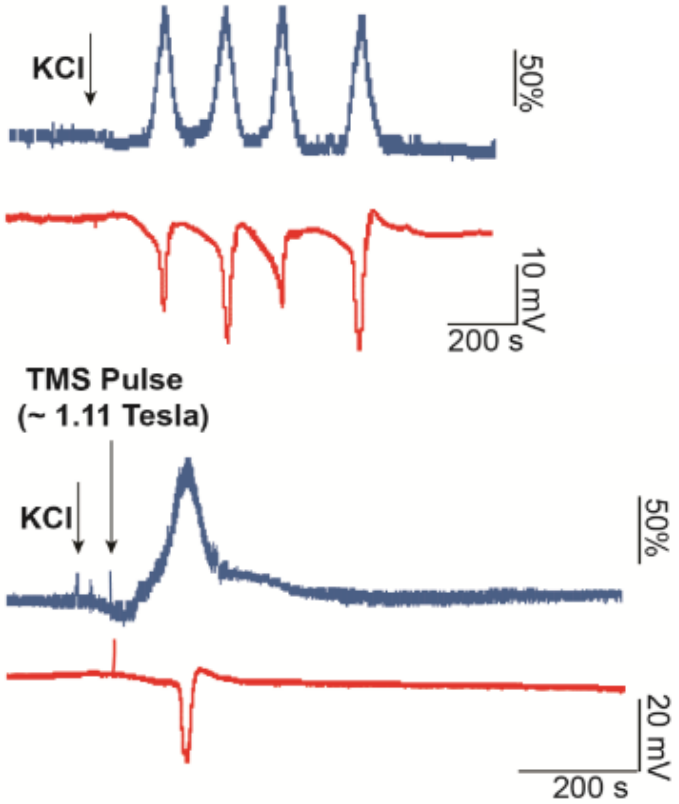
sTMS mini

- FDA cleared for both acute and preventive treatment of migraine
- **Acute:** three sequential pulses at the onset of migraine pain
  - If needed, two additional treatments of three pulses each can be used at 15-minute intervals
- **Prevention:** four pulses twice daily (two consecutive pulses, wait 15 minutes, then repeat the two consecutive pulses)

http://www.eneura.com/wp-content/uploads/2017/03/sTMS-mini-Physicians-Instructions-for-Use-Rev-E.pdf [accessed February 22, 2019].

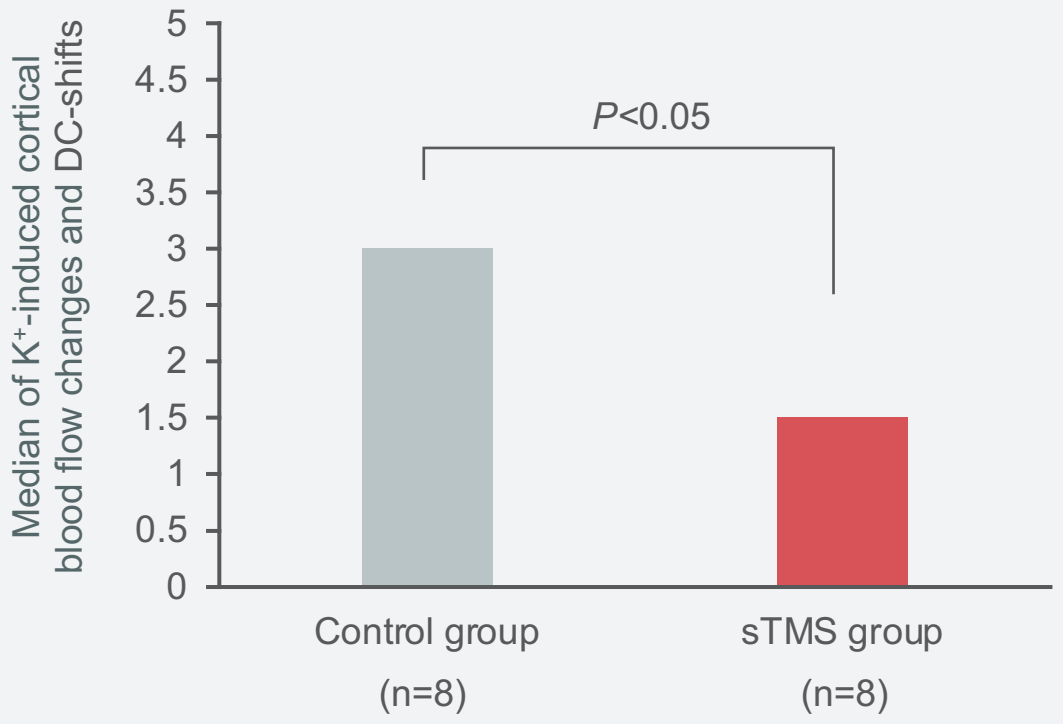
Potential mechanism of action of sTMS

CSD waves induced by topical KCl application in rat cortex



Untreated animal

Animal treated with sTMS

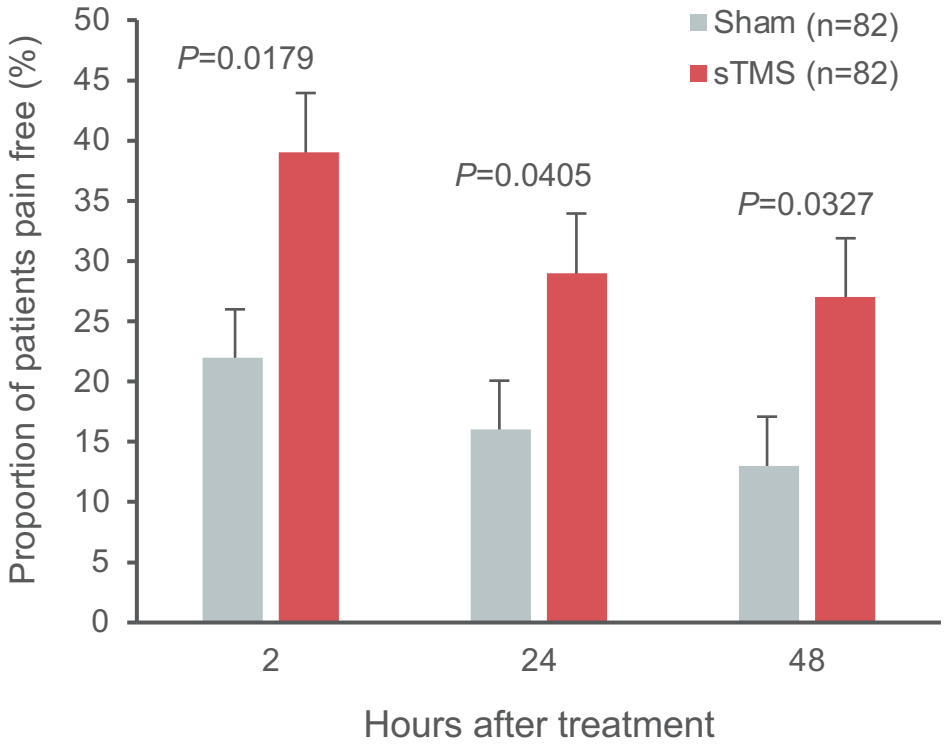


CSD, cortical spreading depression; DC, direct current; K^+, potassium; KCl, potassium chloride.

Andreou AP et al. *Brain*. 2016;139:2002–2014.

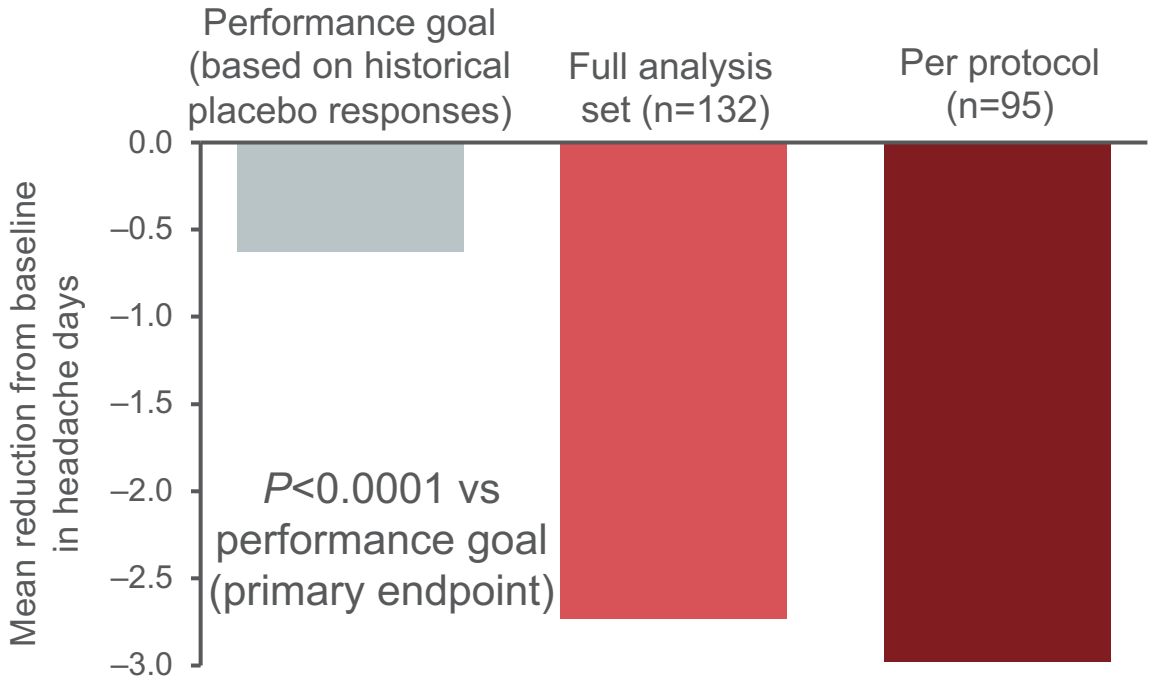
sTMS for treatment of migraine

Acute[1]



- Treatment-related AEs were minimal and mild (5% sTMS vs 2% sham)
- No device-related serious AEs were reported

Preventive[2]



- 42 patients (19%) reported treatment-related AEs (most common: lightheadedness, 4%)
- No serious AEs were reported

1. Lipton RB et al. *Lancet Neurol*. 2010;9:373–380. 2. Starling AJ et al. *Cephalalgia*. 2018;38(6):1038–1048.

sTMS in medication overuse headache

- Patients (N=28) with migraine and medication overuse used sTMS as both preventive and acute treatment for ≥3 months
- Acute medication use days decreased at 12 weeks in 75% of patients
- Reductions in acute medication use maintained in 84% of patients with 6-month data
- No AEs reported

Bhola R et al. *Cephalalgia*. 2015;35(6S):24.

Non-invasive vagus nerve stimulation (nVNS)

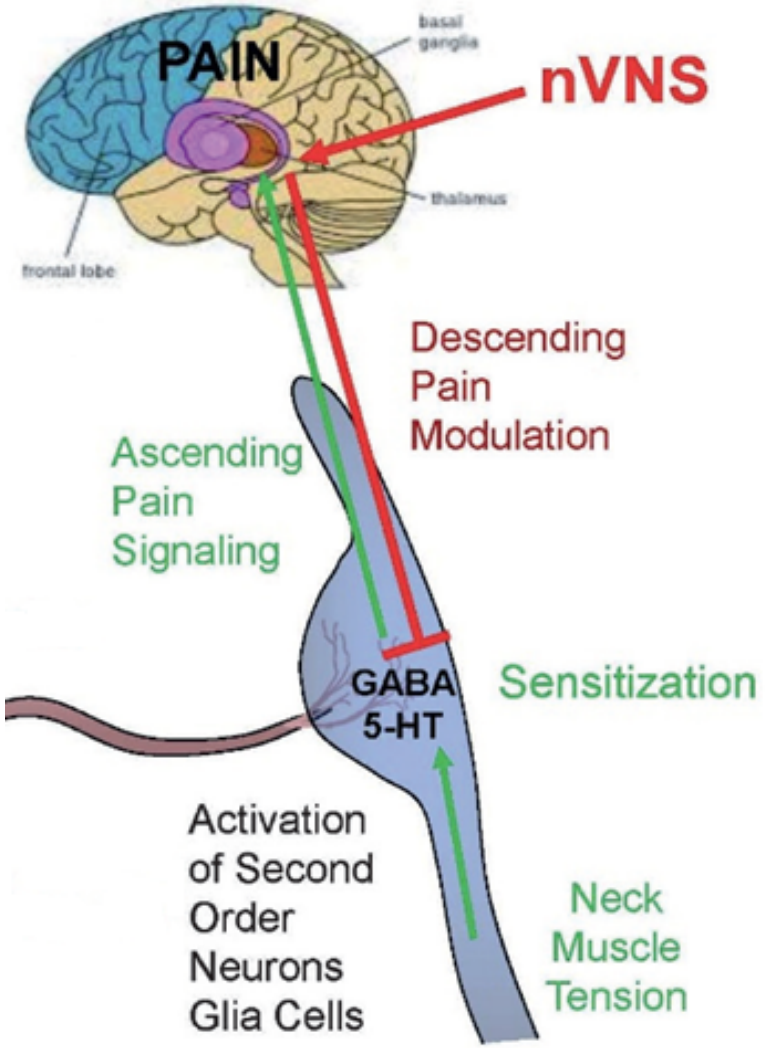
gammaCore Sapphire

- FDA cleared for acute and preventive treatment of migraine
  - Also cleared for acute treatment of episodic cluster headache and adjunctive preventive treatment of cluster headache
- **Acute:** up to 3 treatments, each comprising 2 consecutive 2-minute stimulations applied to either side of the neck

https://www.gammacore.com/wp-content/themes/gammacore-p2/pdf/gammacore_IFU.pdf [accessed February 22, 2019].

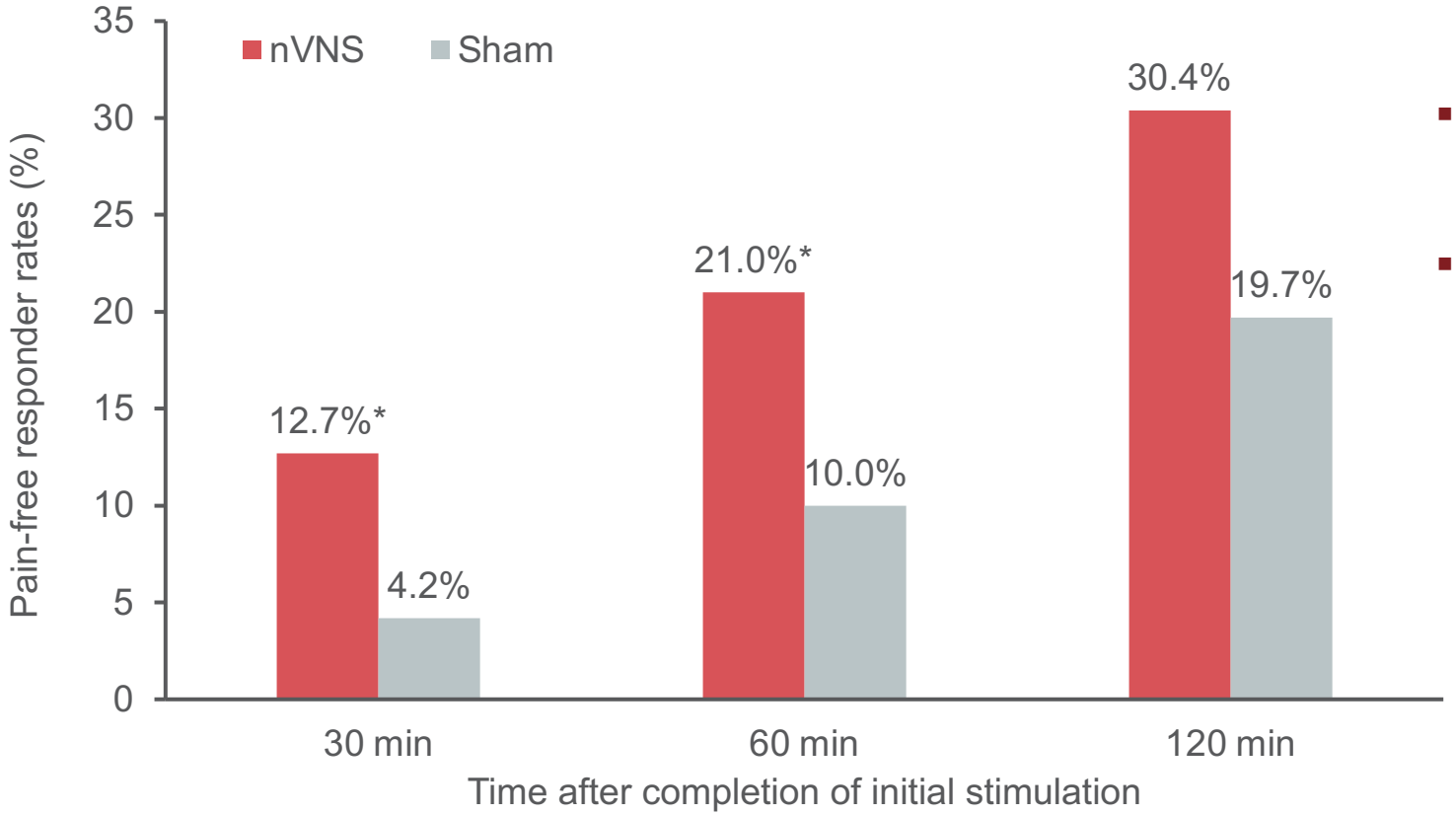
Non-invasive vagus nerve stimulation (nVNS)

nVNS inhibits trigeminal activation via a mechanism involving enhanced descending pain modulation to prevent ascending nociceptive transmission



Durham P et al. *Headache*. 2019;59(Suppl 1):8.

Efficacy of nVNS for acute treatment of migraine



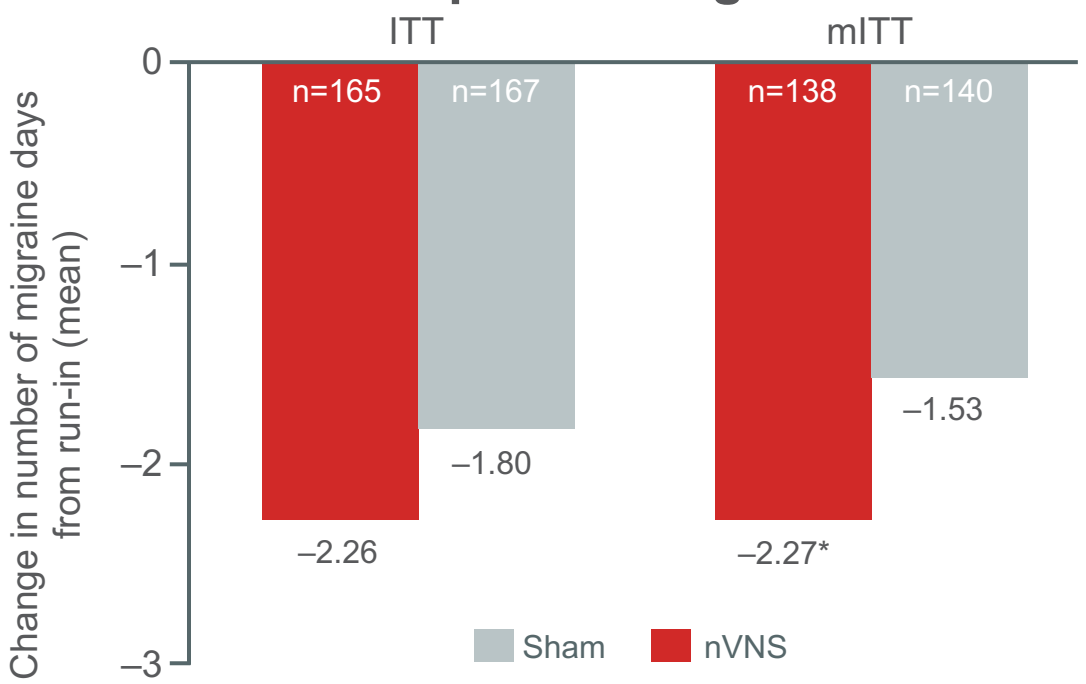
- The incidence of device-related AEs was similar in both groups (6% nVNS vs 8% sham); none was serious
- Application site reactions were the most common device-related AEs in both groups

A total of 248 participants with EM with/without aura were randomized to receive nVNS or sham within 20 minutes of pain onset. Participants were to repeat treatment if pain had not improved in 15 minutes. *P<0.05.
EM, episodic migraine; RCT, randomized controlled trial.

Tassorelli C et al. *Neurology*. 2018;91(4):e364–e373.

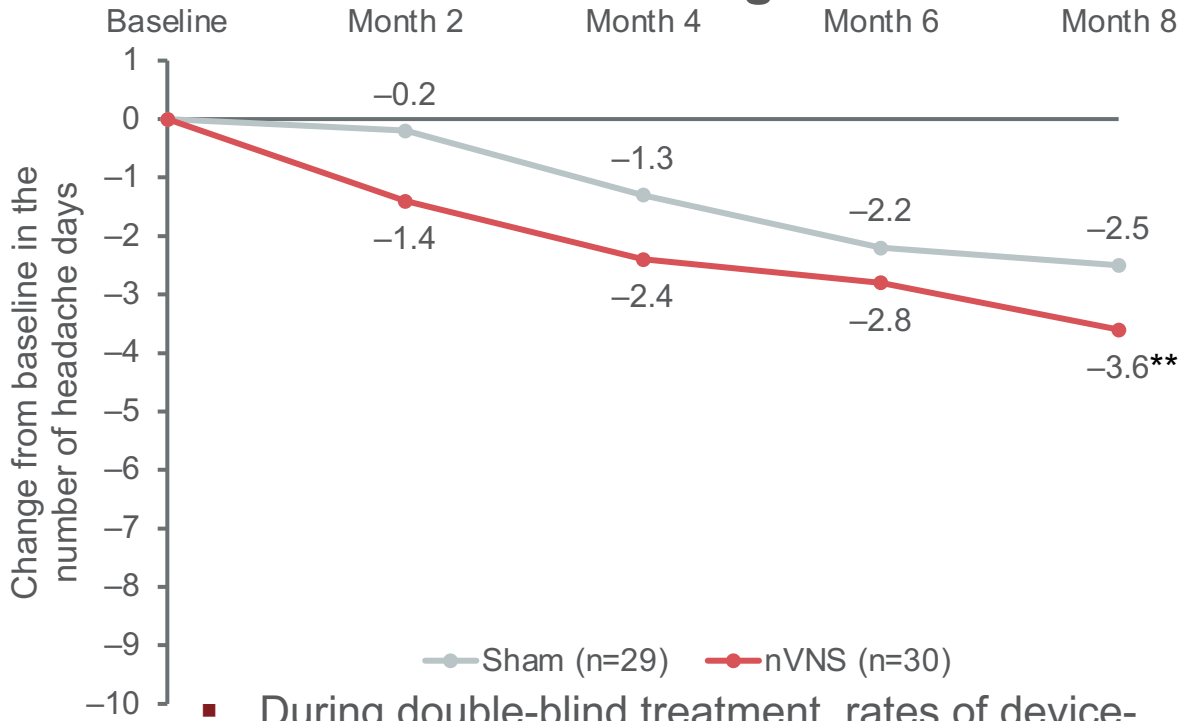
nVNS for prevention of migraine: efficacy results

Episodic migraine[1]



- Device-related AEs (18% nVNS vs 33% sham) were mostly mild and transient; none was serious
- Application site discomfort was the most common

Chronic migraine[2]

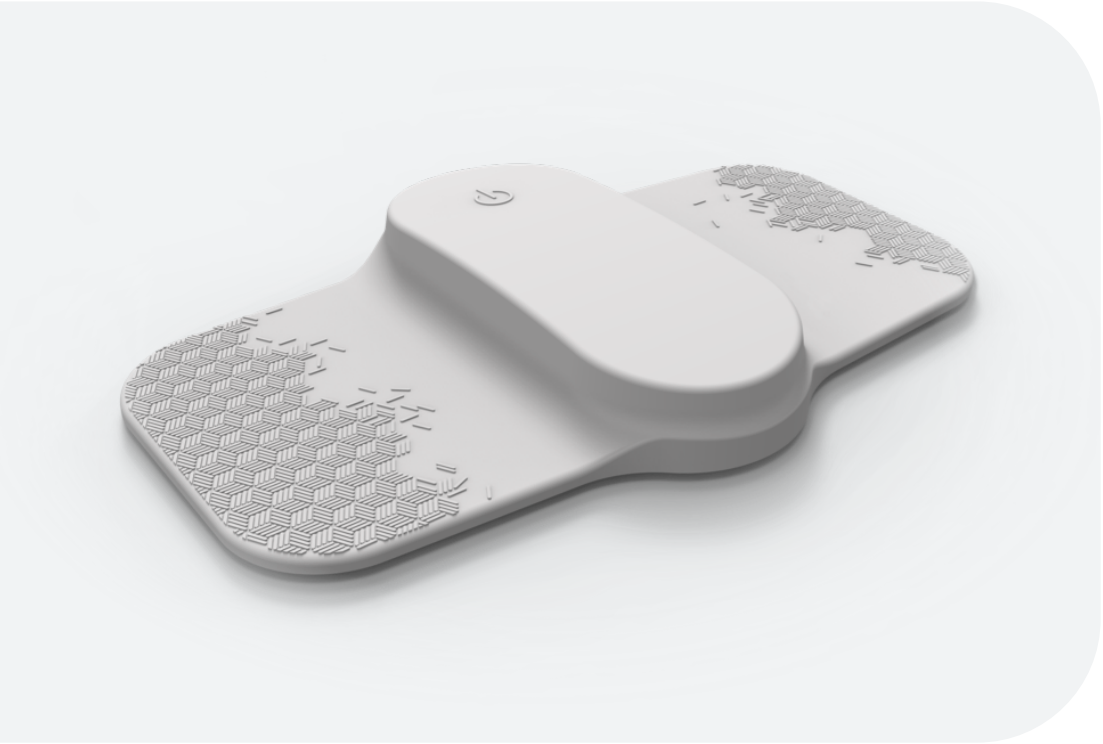


- During double-blind treatment, rates of device-related AEs were similar with nVNS (20%) and sham (17%), mostly mild/moderate and transient, and none was serious

Modified intention-to-treat (mITT) post hoc analysis included patients who were ≥67% adherent. **P*<0.05 vs sham. ***P*<0.05 vs baseline.

1. Diener HC et al. *Cephalalgia*. 2019;39::1475-1487. 2. Silberstein SD et al. *Neurology*. 2016;87:529–538.

Remote electrical neuromodulation (REN)

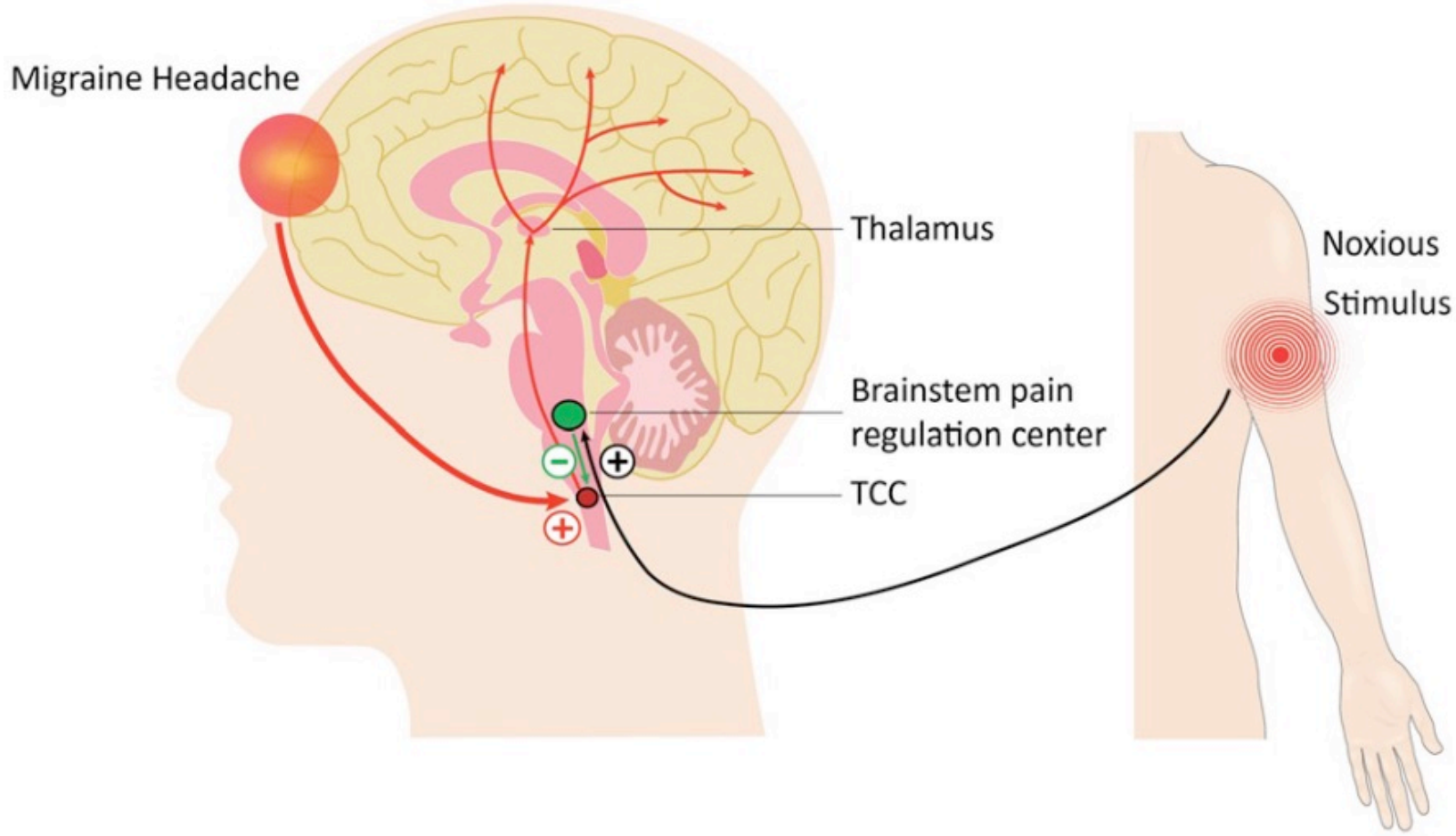


Nerivio

- FDA cleared for acute treatment of migraine in adults without chronic migraine
- **Acute:** The 45-minute treatment should be started as early as possible, and no later than 60 minutes, after onset of headache or aura. The patient adjusts treatment intensity using a smartphone app such that it feels strong yet comfortable (not painful)
- Note: Each device is effective for 12 treatments of 45 minutes

https://theranica.com/nerivio-professional/ [accessed October 11, 2019].

Mechanism of action of REN



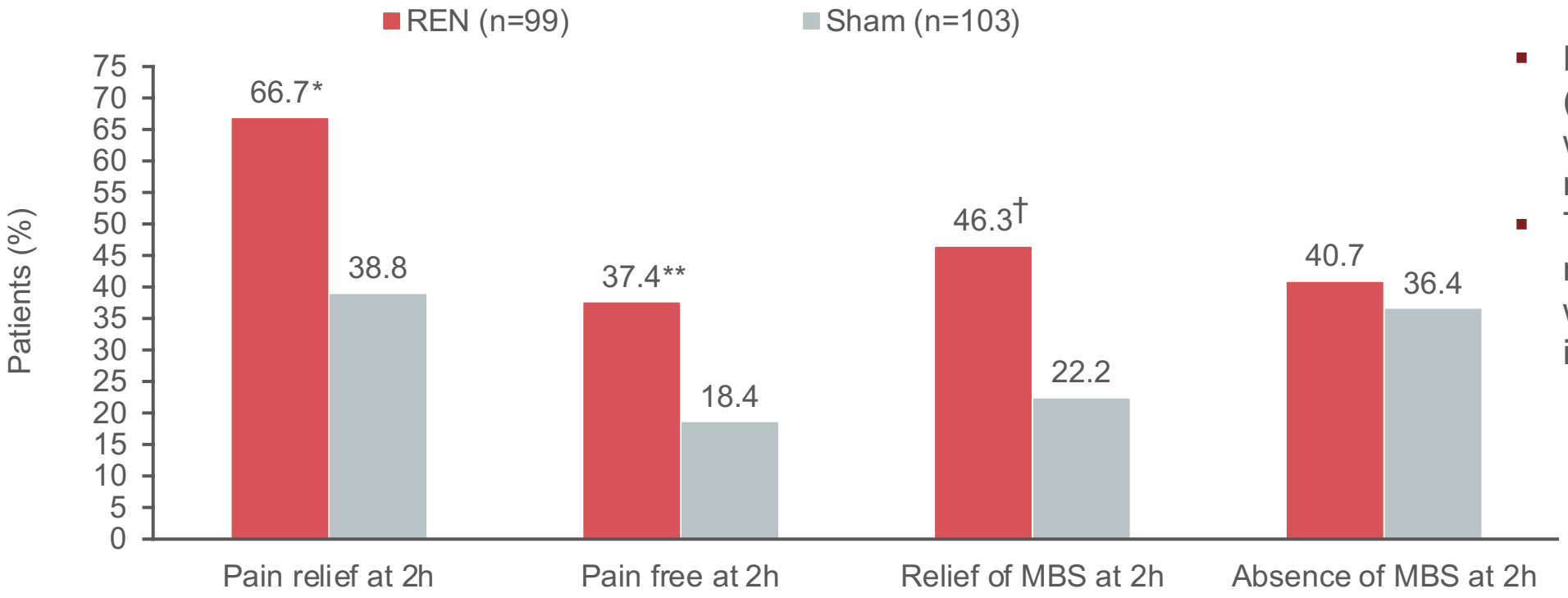
REN stimulates upper arm peripheral nerves to induce conditioned pain modulation

In this endogenous analgesia mechanism, conditioning stimulation inhibits pain in remote body regions

TCC, trigeminal cervical complex.

Yarnitsky D et al. *Headache*. 2019;59(8):1240–1252.

Efficacy of REN for acute treatment of migraine

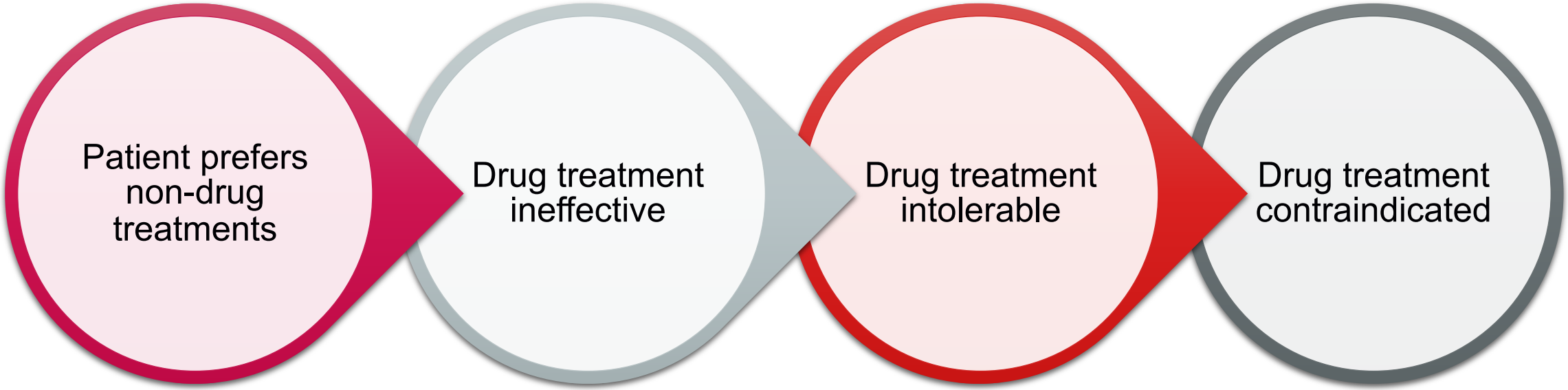


- Device-related AEs (4.8% REN vs 2.4% sham) were all mild and transient; none was serious
- The most common device-related AEs included warmth sensation and pain in the arm

*P<0.0001. **P<0.01. †P<0.001 vs placebo.
Patients were randomized to active REN or sham treatment; 202 used the study treatment within 1 hour of onset and had evaluable 2-hour pain data.
2h, 2 hours; MBS, most bothersome symptom.

Yarnitsky D et al. *Headache*. 2019;59(8):1240–1252.

AHS recommends non-drug acute migraine treatment when:



American Headache Society (AHS). *Headache*. 2019;59:1–18.

Neuromodulatory Approaches Summary

- A number of neurostimulation approaches are relevant to migraine
- Non-invasive forms of treatment are preferred
- Several neuromodulation devices have been approved for acute and/or preventive treatment of migraine
- Neuromodulation has the potential to reduce acute medication overuse
- Tolerability and safety are major advantages
- Cost and access continue to be challenges