PainWeek®

Interventional Options for Refractory Migraines and Cervicogenic Headaches

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Title & Affiliation

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Learning Objectives

- Describe the symptoms associated with cervicogenic headache
- List the mechanisms of pain referral associated with cervicogenic headache
- Describe migraine and migraine subtypes
- Describe standard and alternative treatment options for migraine
- Cite the most recent findings of peripheral nerve stimulation for migraine

Disclosure

- The author declares NO conflict of interest.

Cervicogenic Headaches

Cervicogenic Headache

- Common **chronic and recurrent headache** that usually starts after neck movement and presents as **unilateral pain that starts in the neck**
- Usually accompanies a **reduced range of motion (ROM) of the neck**
- **Diagnostic criteria** must include all the following points:
  1. Source of the pain must be in the neck and perceived in head or face.
  2. Evidence that the pain can be attributed to the neck. It must have 1 of the following: demonstration of clinical signs that implicate a source of pain in the neck or abolition of a headache following diagnostic blockade of a cervical structure or its nerve supply using a placebo or other adequate controls.
  3. Pain resolves within 3 months after successful treatment of the causative disorder or lesion.

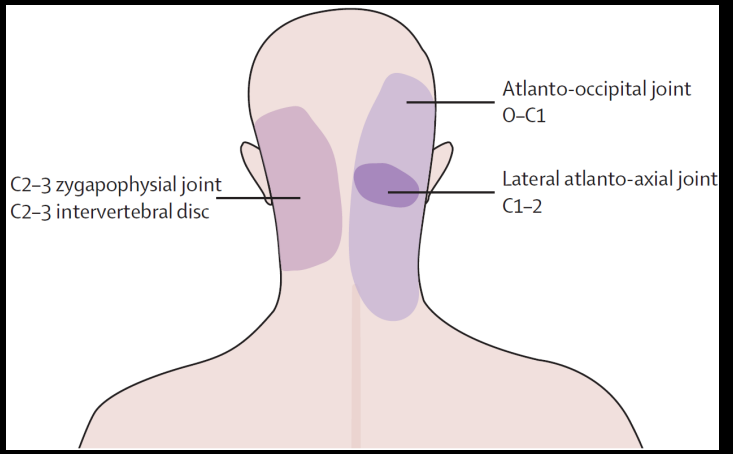
Cervicogenic Headache

- **Epidemiology**
  - Rare chronic headache in people who are 30 to 44 years old
  - Prevalence among patients with headaches is 1% to 4%, depending on how many criteria fulfilled and based on many different studies
  - Affects males and females about the same with a ratio of 0.97 (F/M ratio)
  - Age at onset is thought to be the early 30s, but the age the patients seek medical attention and diagnosis is 49.4
  - When compared with other headache patients, these patients have a pericranial muscle tenderness on the painful side and a significantly reduced cervicogenic headache

Cervicogenic Headache

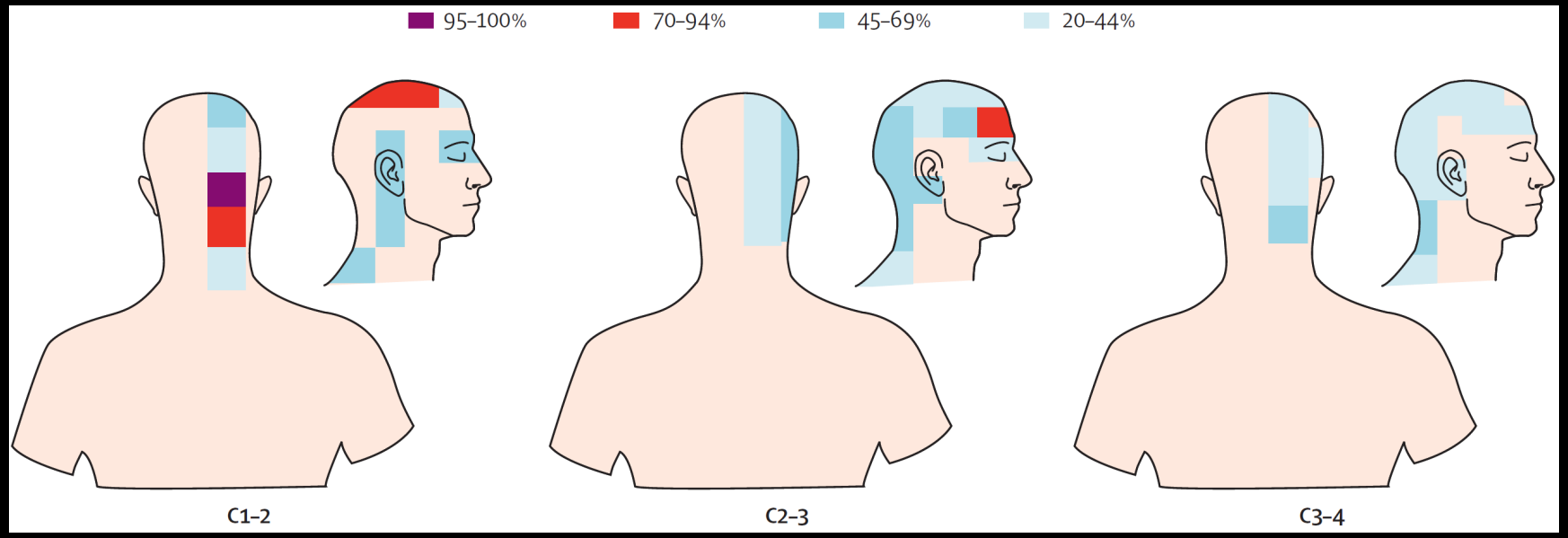
- **Etiology**
  - Referred pain arising from irritation caused by cervical structures innervated by spinal nerves C1, C2, and C3
  - Any structure innervated by the C1–C3 spinal nerves could be the source for a cervicogenic headache

	Innervation		
Structure	**C1**	**C2**	**C3**
Joints	Atlanto-occipital	Median Atlantoaxial	
		Lateral Atlantoaxial	C2-C3 zygapophyseal
			C2-C3 Disc
Muscles	Suboccipital	Prevertebral; sternocleidomastoid, trapezius	
		Semispinalis, splenius	
			Multifidus; semispinalis
Ligaments	Transverse atlantoaxial and alar; membrana tectoria		
Arteries	Vertebral; internal carotid		
Dura	Upper spinal cord; posterior cranial fossa		



Pain Physician: March/April 2015; 18:109-130

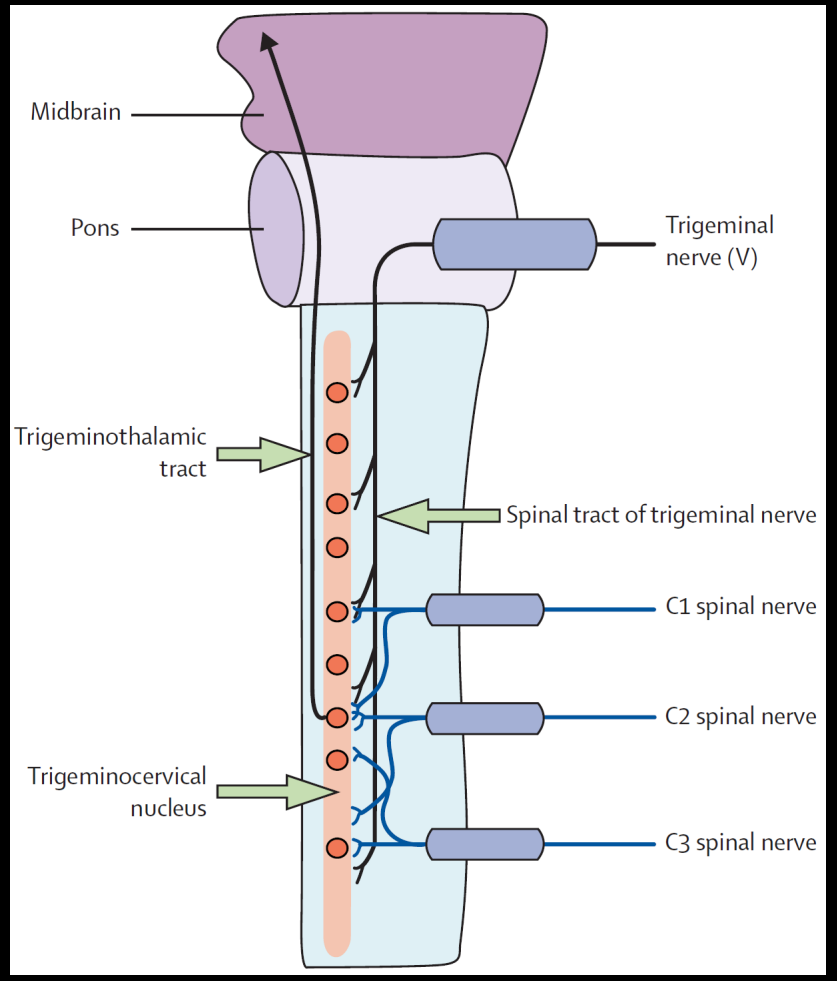
- Areas of pain relief in patients who underwent controlled blocks of the synovial joints at C1–2, C2–3, and C3–4
- Density of shading is proportional to number of patients who perceived pain in particular area indicated



- Pain from the lateral atlanto-axial joint (C1–2) tends to be focused on the occipital and suboccipital regions, and tends to be referred to the vertex, orbit, and ear
- Pain from the C2–3 zygapophysial joint also occurs in the occipital region and spreads across the parietal region to the frontal region and orbit
- Pain from the C3–4 joint can be referred to the head but is more commonly focused in the upper and lateral cervical region

Cervicogenic Headache

- **Mechanism of pain referral from the cervical spine to the head**
  - Anatomical convergence of pain fibers from the trigeminal nerve (including the ophthalmic division) and the upper 3 cervical nerves forms the basis for pain to be referred from the upper cervical region to the head, including radiation to the frontal and periorbital regions.
  - The trigeminocervical nucleus receives not only the C1–C3 afferents but also the first branch of the trigeminal sensory afferents, indicating that it receives second-order neuron afferents from the trigeminal and upper 3 cervical spinal nerves.



Headache Disorders

Primary Headache Disorders

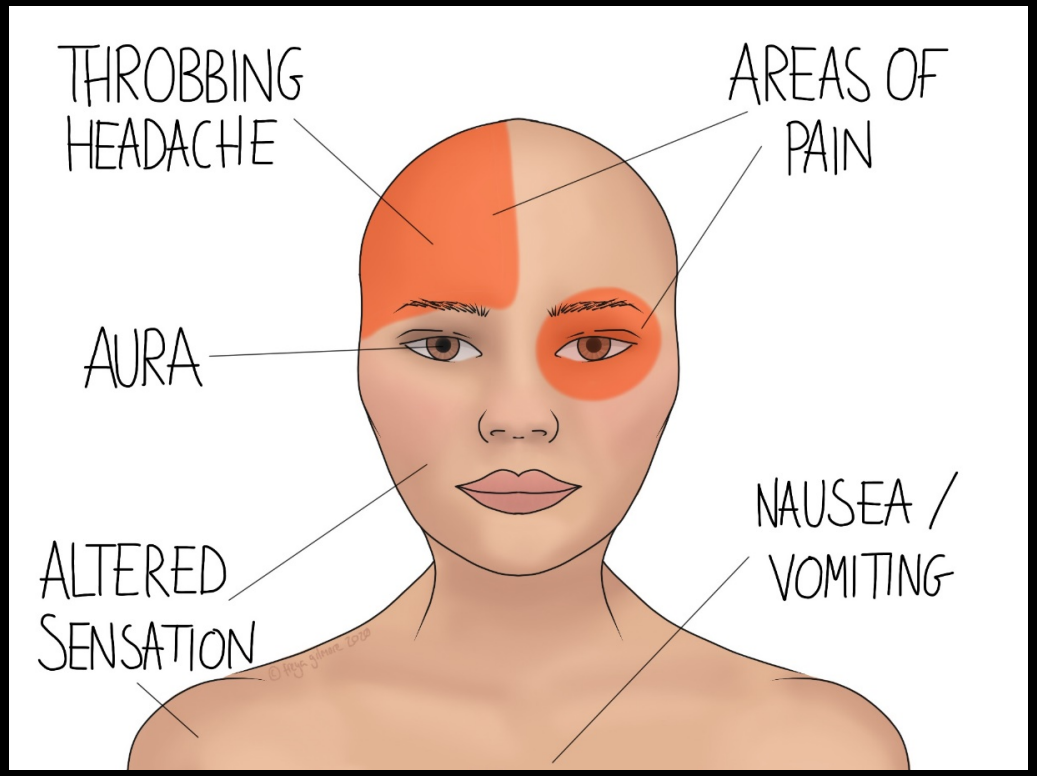
1. Migraine
2. Tension-type headache with pericranial tenderness

Secondary Headache Disorders

1. Headache associated with Cranio-cervical dystonia
2. Headache attributed to Chiari malformation
3. Headache attributed to cervical carotid or vertebral artery dissection
4. Headache attributed to whiplash
5. Cervicogenic headache

Current Pain and Headache Reports (2018) 22: 47

Clinical features	Migraine	TTH	CGH	ON
Cervical spine or neck soft tissue lesion			+	
Exacerbated by movement	+		+	
Responds to diagnostic block of cervical structure or its nerve supply			+	
Posterior head and neck pain	+	+	+	+
Myofascial trigger points	+	+	+	+
Migraine features	+		+	
Response to greater and lesser occipital nerve blockade	+		+	+


THROBBING HEADACHE
AREAS OF PAIN
AURA
ALTERED SENSATION
NAUSEA / VOMITING

Migraines

Migraines

- Complex disorder characterized by **episodes of moderate-to-severe headache** that may unfold over hours to days
- Strong genetic component
- Presentation is **most often unilateral** and generally associated with nausea and increased sensitivity to light and sound

- **Epidemiology**
  - Highly prevalent condition, affecting 12% of the population, affecting up to 17% of women and 6% of men each year
  - Second leading cause of disability worldwide
  - Fourth or fifth most common reason for emergency visits accounting for an annual 3% of all emergency visits
  - Prevalence increases in puberty but continues to increase until 35 to 39 years of age, decreasing later in life, especially after menopause

Proposed Criteria for Refractory Chronic Migraine

Criteria	Definition
A. Primary Diagnosis	1. ICHD-III chronic migraine 2. Medication overuse headache excluded[a]
B. Refractory	Failure to respond to 5 classes of preventive treatments (including 2 from 1 to 3[b]): 1. Topiramate 2. Minimum of two quarterly injections of Onabotulinumtoxin A 3. CGRP pathway monoclonal antibody 4. Betablockers (Propranolol, Metoprolol, Timolol) 5. Tricyclic antidepressant (Amitriptyline) 6. SNRI (Venlafaxine) 7. Sodium valproate/Divalproex sodium 8. Other pharmacological preventive treatments with established efficacy in migraine[c]
C. Adequate Trial	At least 2 month trial at an optimum or maximum tolerated dose (excluding the time taken for the titration o the dose), unless terminated early due to side effects[d]
D. Failed Trial	1. Failure to respond to drug (< 50% reduction in frequency and/or severity of monthly migraine days) 2. Intolerable side effects 3. Contraindication to use

A. Patients who overuse abortive treatments can be included provided medication overuse headache has been excluded
B. Applicable if available in the local healthcare system
C. 2 class I or 2 class II based on American Academy of Neurology Scheme for classification of evidence
D. Optimum dose defined as that used in the controlled trials demonstrating efficacy or as outlined by local treatment guidelines

Migraine Subtypes

- **Migraine without aura**: recurrent headache attack of 4 to 72 hours; most common type of migraine (75%); typically unilateral in location, pulsating in quality, moderate to severe in intensity, aggravated by physical activity, and associated with nausea and light and sound sensitivity (photophobia and phonophobia)
- **Migraine with aura**: recurrent fully reversible attacks, lasting minutes, of typically one or more of these unilateral symptoms: visual, sensory, speech and language, motor, brainstem, and retinal, usually followed by headache and migraine symptoms
- **Chronic migraine**: occurs on 15 or more days in a month for more than 3 months and has migraine features on at least 8 or more days in a month
- **Probable migraine**: symptomatic migraine attack that lacks 1 of the features required to fulfill criteria for 1 of the above and does not meet the criteria for another type of headache

Migraine Etiology

- **Genetic Component**
  - The risk of migraines in ill relatives is 3 times greater than that of relatives of non-ill subjects, but there has not been any pattern of inheritance identified
  - The genetic basis of migraine is complex, and it is uncertain which loci and genes are the ones implicated in the pathogenesis; it may be based on more than one genetic source at different genomic locations acting in tandem with environmental factors to bring susceptibility and the characteristics of the disease in such individuals
  - The identification of these genes in an individual with migraines could predict the targeted prophylactic treatment

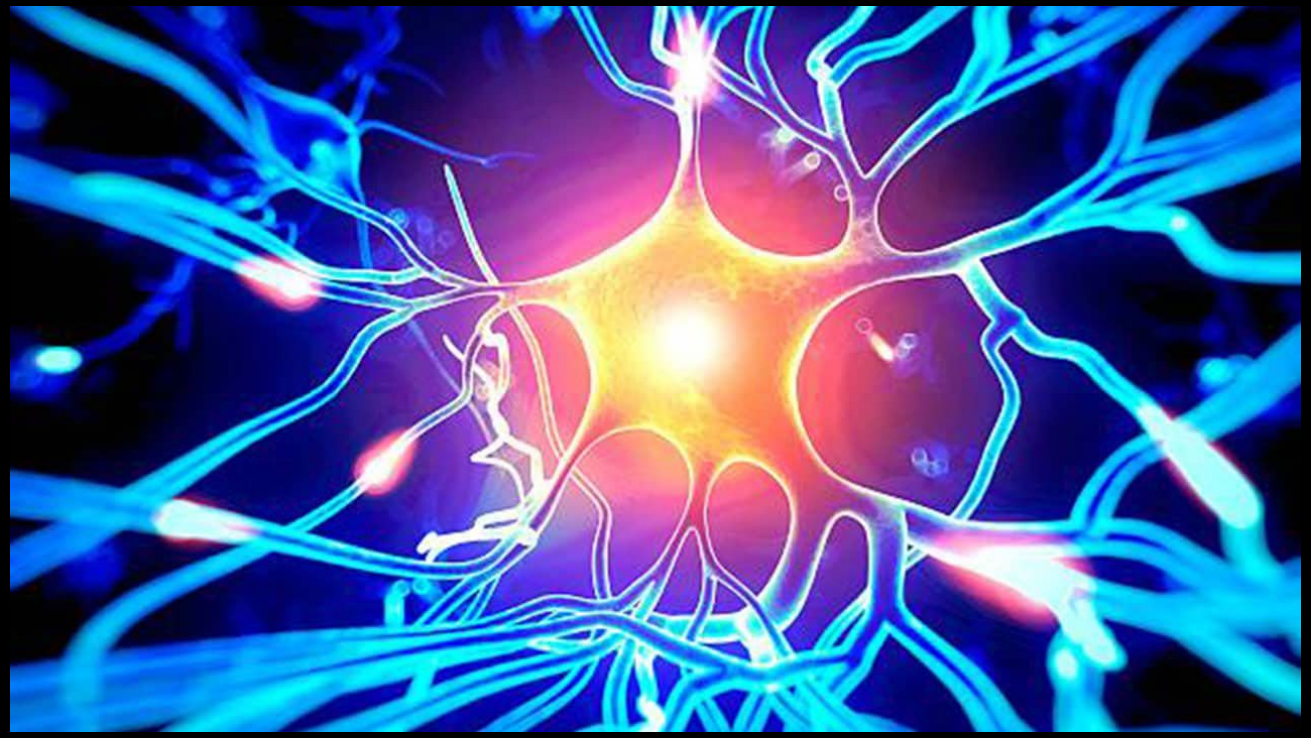
Migraine Triggers

- **A retrospective study found that 76% of the patients reported triggers:**
  - **Stress** in 80% (probable factor)
  - **Hormonal changes** in 65% during menstruation, ovulation, and pregnancy (probable factor)
  - **Skipped meals** in 57% (probable factor)
  - **Weather changes** in 53% (probable factor)
  - **Excessive or insufficient sleep** in 50% (possible factor)
  - **Odors** in 40% (perfumes, colognes, petroleum distillates)
  - **Neck pain** in 38%
  - **Exposure to lights** in 38% (probable factor)
  - **Alcohol ingestion** in 38% (wine as a probable factor)
  - **Smoking** in 36% (unproven factor)
  - **Late sleeping** in 32%
  - **Heat** in 30%
  - **Food** in 27% (aspartame as a possible factor, and tyramine and chocolate as unproven factors)
  - **Exercise** in 22%
  - **Sexual activity** in 5%

Refractory Migraine Treatment Options

	Oral/Nasal	Injectable	Neurostimulation
Acute	• Oral and Intranasal Triptans • High dose NSAIDS • Paracetamol • Antiemetics	• Subcutaneous sumatriptan	• Transcranial magnetic stimulation • External trigeminal nerve stimulation (Cefaly) • Vagal nerve stimulation
Preventive	• Beta-blockers: Propranolol, Metoprolol, Timolol, Atenolol, Nadolol • Anticonvulsants: Topiramate, Valproate • Tricyclics: Amitriptyline • SNRI: Venlafaxine • Angiotensin pathway blockers: Lisinopril, Candesartan • Calcium channel blockers: Flunarizine • Nutraceuticals: Riboflavin, Coenzyme Q10, Magnesium, Feverfew	• Onabotulinumtoxin A • CGRP-pathway monoclonal antibodies	• External trigeminal nerve stimulation (Cefaly) • Transcranial magnetic stimulation • Occipital nerve stimulation • High cervical spinal cord stimulation
Transitional	• Corticosteroids	• Greater occipital nerve block • Multiple cranial nerve blocks • Intravenous dihydroergotamine • Intravenous lidocaine	

D'Antona and Matharu *The Journal of Headache and Pain* (2019) 20:89



Interventional Options for Refractory Migraines
Nerve Blocks

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Chronic Headache: a Review of Interventional Treatment Strategies in Headache Management

Ruchir Gupta [1] · Kyle Fisher [2,3] · Srinivas Pyati [2,3]

Current Pain and Headache Reports (2019) 23: 68

- Some forms of headaches remain **intractable to conservative therapies**, for instance due to resistance to common regimens, intolerance to pharmaceutical agents, or comorbid factors that cause interactions with their therapies
- Interventional treatment options will differ depending on the cause of a headache

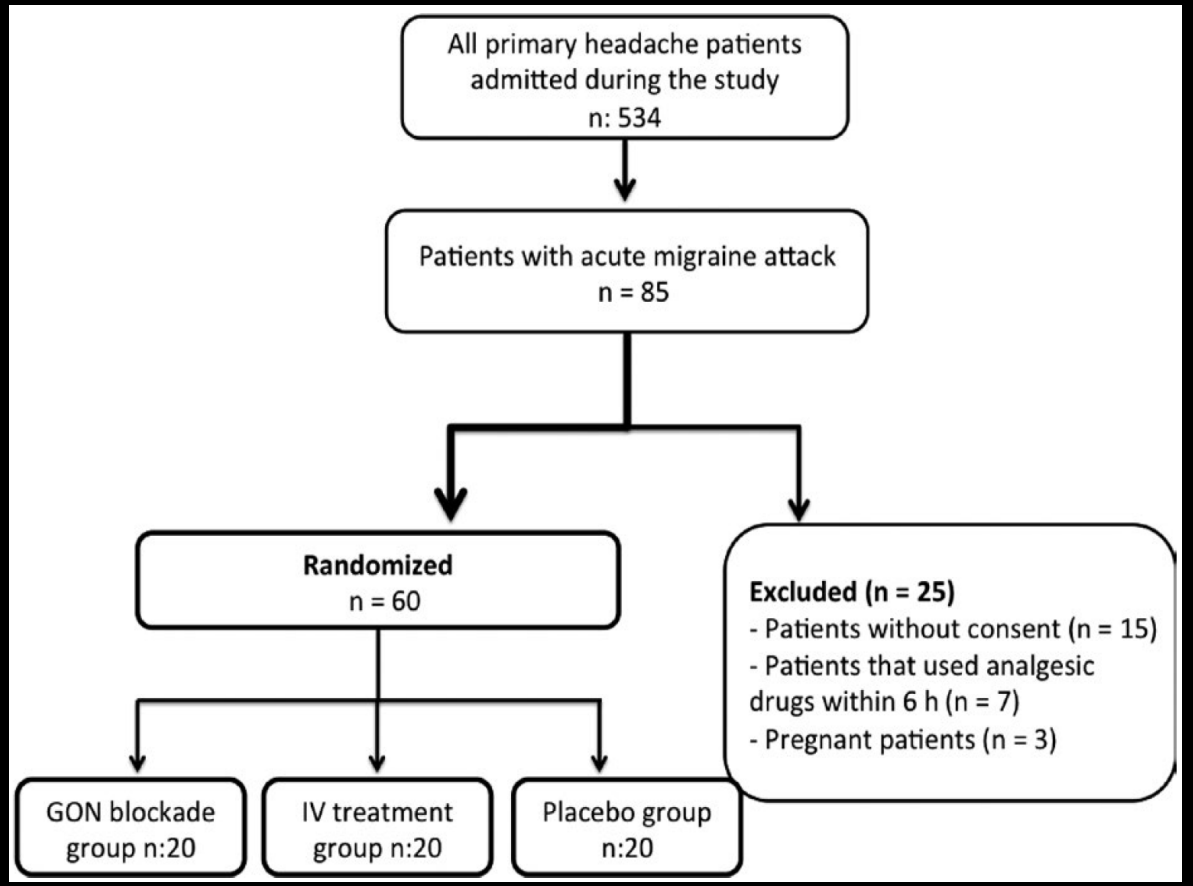
Interventional treatment options
Peripheral nerve stimulation (PNS)
Third occipital nerve (TON) block
Lesser occipital nerve (LON) and greater occipital nerve (GON) blocks
Sphenopalatine ganglion (SPG) block
Radiofrequency ablation (RFA)
Cervical epidural steroid injections (CESI)

The effectiveness of greater occipital nerve blockade in treating acute migraine-related headaches in emergency departments

Acta Neurol Scand. 2018;1–7.

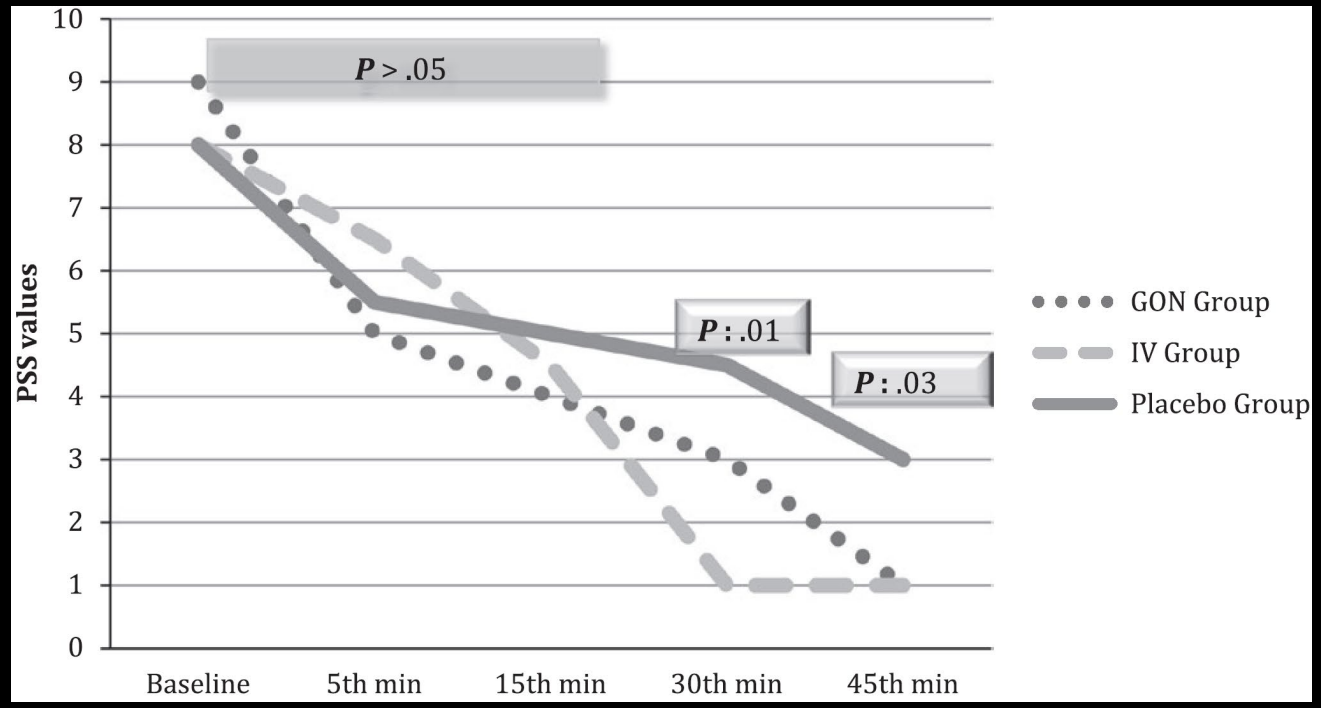
O. Korucu[1] | S. Dagar[2] | Ş. K. Çorbacioglu[2] | E. Emektar[2] | Y. Cevik[2]

- Objective: **evaluate the effectiveness of a greater occipital nerve (GON) blockade** among patients admitted to the emergency department with acute migraine headaches
- **Prospective-randomized controlled study on 60 patients**:
  - GON blockade group (nerve blockade with bupivacaine)
  - Placebo group (injection of normal saline into the GON area)
  - Intravenous (IV) treatment group (IV dexketoprofen and metoclopramide)



PSS [median (IQR 25%-75%)]	GON blockade group (n = 20)	IV treatment group (n = 20)	Placebo group(n = 20)	*P*
Baseline	9 (7.25-9.75)	8 (7-9)	8 (7-9.5)	.2
5th min	5 (3.25-8)	6.5 (5-7)	5.5 (5-7)	.7
15th min	4 (0-6.5)	4.5 (2.3-5)	5 (3-6)	.3
30th min	3 (0-4.75)	1 (0-4)	4.5 (1-6)	.01
45th min	1 (0-3)	1 (0-2)	3 (1-5.75)	.03

PSS, pain scale score; IQR, interquartile range; GON, greater occipital nerve; IV, intravenous.



- Pain scale score of patients throughout time according to groups
- Pain scale score change in patients throughout time according to groups

Acta Neurol Scand. 2018;1–7.

Acta Neurol Scand. 2018;1–7.

- **Results**
- Mean decreases in the 5-, 15-, 30-, and 45-minutes pain scale scores were greater in the GON blockade group than in the dexketoprofen and placebo groups
- **GON blockade was as effective as an IV dexketoprofen + metoclopramide treatment and superior to a placebo** in patients with acute migraine headaches

Comparison of the treatment groups by the changes in pain scale score based on duration

	P value*
0-30 min	
GON vs placebo	.012
IV treatment vs placebo	.03
GON vs IV treatment	.56
0-45 min	
GON vs placebo	.016
IV treatment vs placebo	.03
GON vs IV treatment	.39

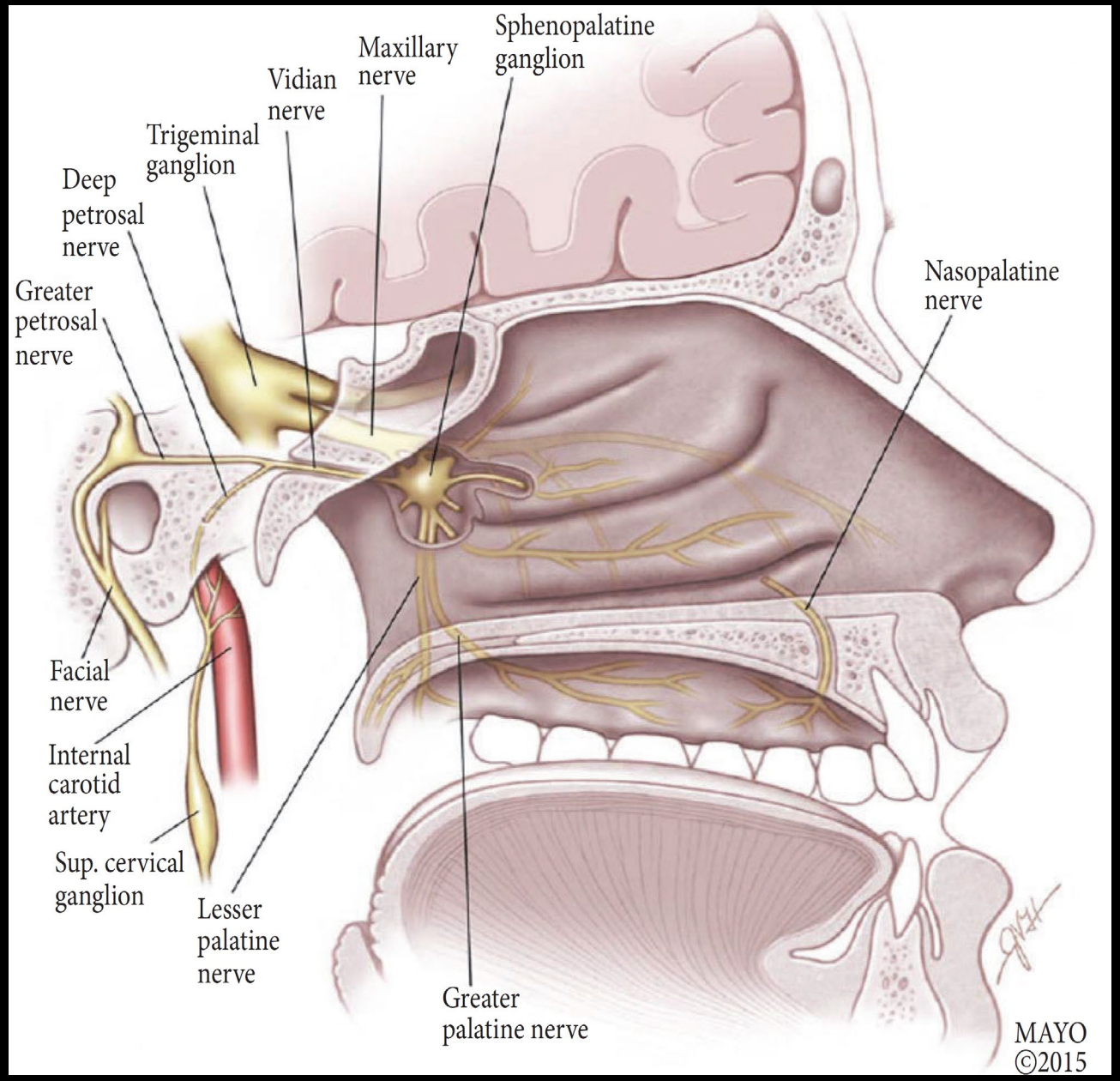
Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache

Mohamed Binfalah,[1] Eman Alghawi,[2] Eslam Shosha,[3] Ali Alhilly,[4] and Moiz Bakhiet[5]

Pain Res Treat. 2018 May 7;2018:2516953.

- Aim: assess the efficacy and safety of **transnasal sphenopalatine ganglion block** in the treatment of acute migraine, n = 55 patients

- Results:
  - The **majority of patients became headache-free at 15 minutes, 2 hours, and 24 hours** after procedure (70.9%, 78.2%, and 70.4%, respectively)
  - The rate of headache relief (50% or more reduction in headache intensity) was 27.3% at 15 minutes, 20% at 2 hours, and 22.2% at 24 hours
  - The mean pain numeric rating scale decreased significantly at 15 minutes, 2 hours, and 24 hours, respectively
  - Most patients rated the results as very good or good
  - The procedure was **well-tolerated** with few adverse events



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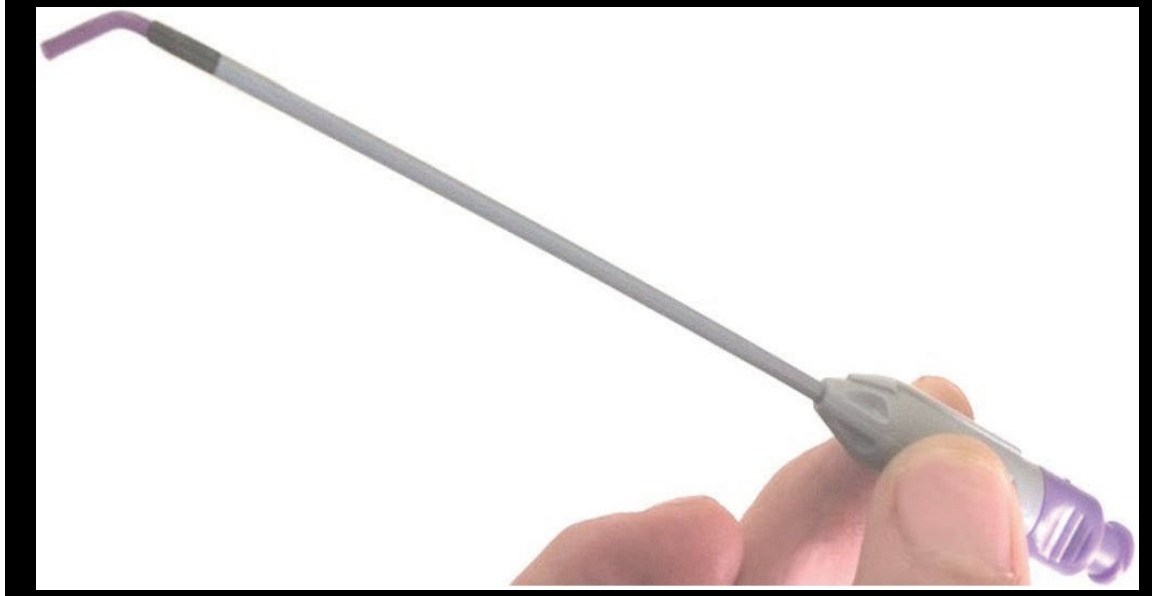
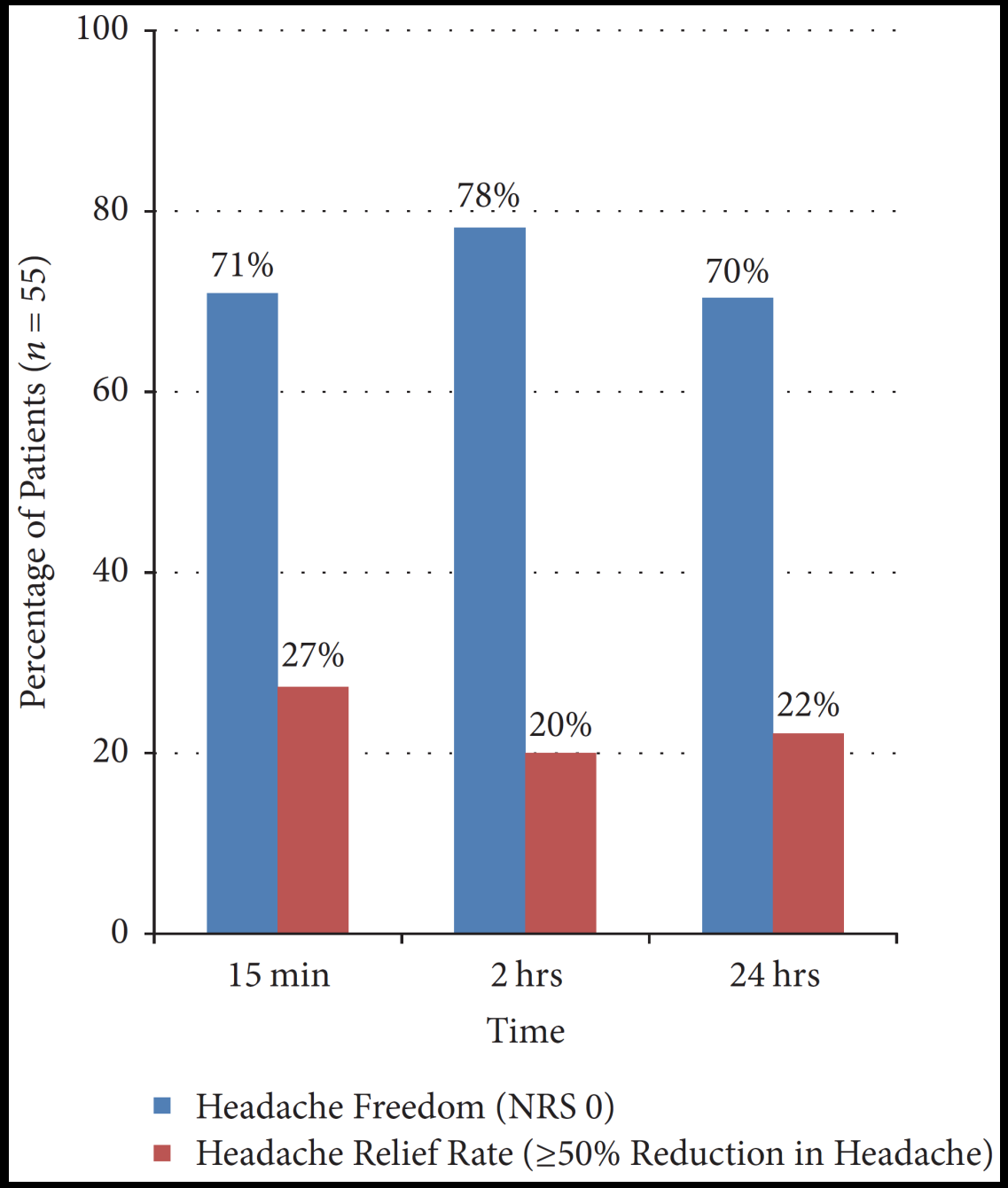
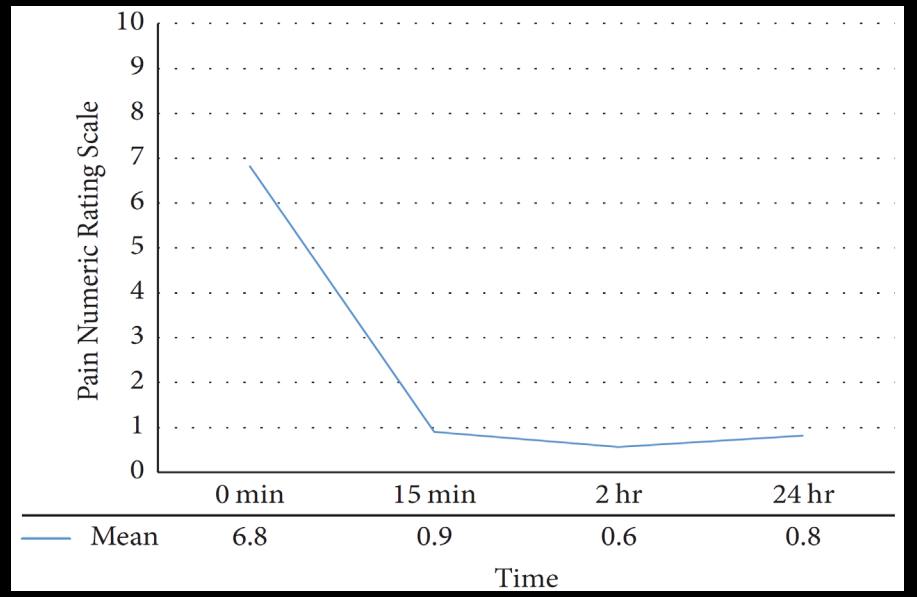
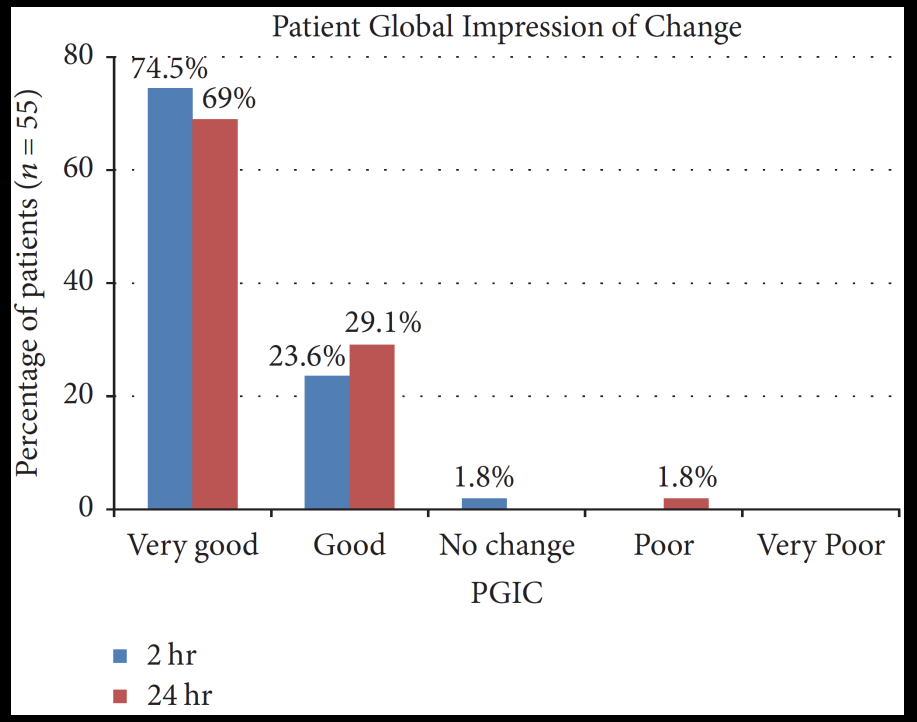


The Sphenocath Device

Sagittal view of the nasopharynx, showing the sphenopalatine ganglion, and its neural connections


100
80
60
40
20
0
Percentage of Patients (n = 55)
71%
27%
78%
20%
70%
22%
15 min
2 hrs
24 hrs
Time
Headache Freedom (NRS 0)
Headache Relief Rate (≥50% Reduction in Headache)


10
9
8
7
6
5
4
3
2
1
0
Pain Numeric Rating Scale
0 min
15 min
2 hr
24 hr
Mean
6.8
0.9
0.6
0.8
Time


Patient Global Impression of Change
80
60
40
20
0
Percentage of patients (n = 55)
74.5%
69%
23.6%
29.1%
1.8%
1.8%
Very good
Good
No change
Poor
Very Poor
PGIC
2 hr
24 hr

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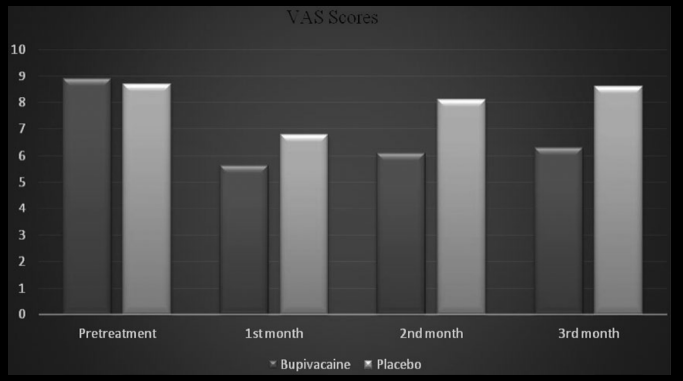
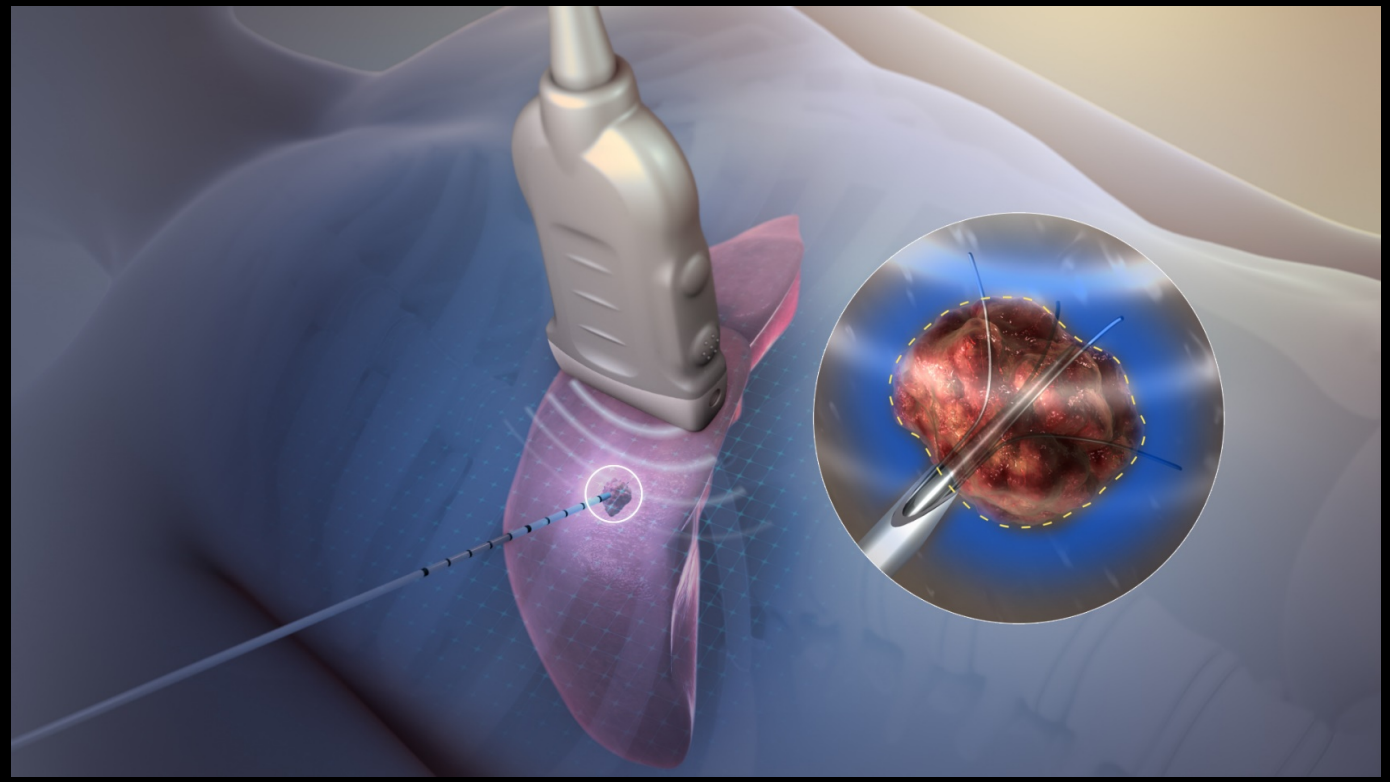
The efficacy of greater occipital nerve blockade in chronic migraine: A placebo-controlled study

Acta Neurol Scand 2016; 1–7

H. L. Gul[1] | A. O. Ozon[2] | O. Karadas[3] | G. Koc[5] | L. E. Inan[4]

- Aim: evaluate the **efficacy of greater occipital nerve (GON)** blockade in **44 patients** with chronic migraine (CM)
- Methods: GON blockade was administered 4 times (once per week) with bupivacaine or saline, for 4 weeks
- **Bupivacaine GON group showed a significant decrease in the frequency of headache and VAS scores** at 1, 2, and 3 months of follow-up
- Saline GON groups showed significant decrease in the frequency of headache and VAS scores at 1 month follow-up, but no significant difference and 2 and 3 months





Interventional Options for Refractory Migraines
Radiofrequency, Steroid Injections

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Randomized, double-blind, comparative-effectiveness study comparing pulsed radiofrequency to steroid injections for occipital neuralgia or migraine with occipital nerve tenderness

Steven P. Cohen[a,*], B. Lee Peterlin[b], Larry Fulton[c], Edward T. Neely[d], Connie Kurihara[e,f], Anita Gupta[g], Jimmy Mali[h], Diana C. Fu[i], Michael B. Jacobs[j], Anthony R. Plunkett[h], Aubrey J. Verdun[k], Milan P. Stojanovic[l], Steven Hanling[m], Octav Constantinescu[n], Ronald L. White[n], Brian C. McLean[o], Paul F. Pasquina[p], and Zirong Zhao[q,r]

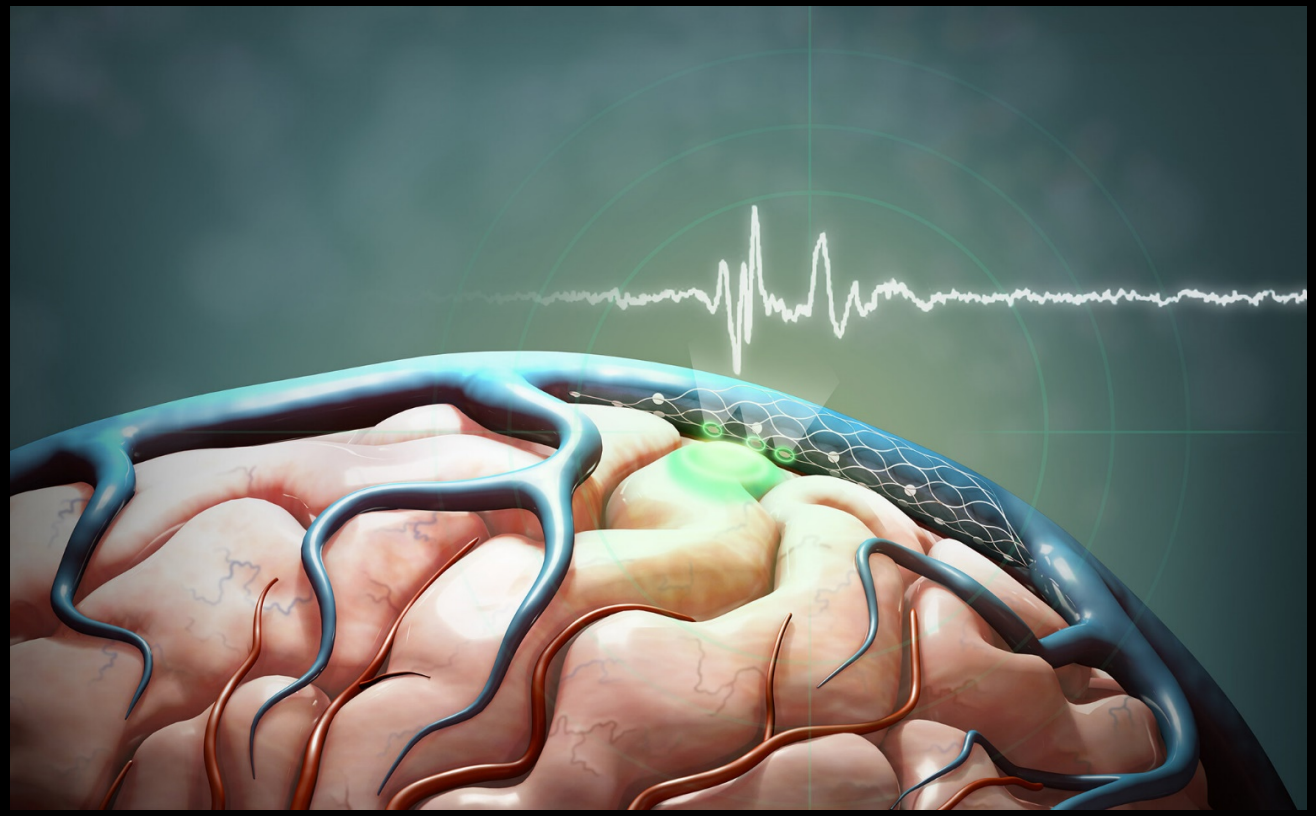
Pain. 2015 December ; 156(12): 2585–2594.

- Objective: **compare pulsed radiofrequency and steroid injections** in **81 participants** with occipital neuralgia or migraine with occipital nerve tenderness
- Results:
  - The **PRF group experienced greater reduction in average occipital pain** at 6 weeks (P <0.001), than the steroid group, which persisted through the 6-month follow-up
  - Comparable benefits favoring PRF were obtained for worst occipital pain through 3 months (P = 0.043), and average overall headache pain through 6 weeks (P = 0.037)
  - Adverse events were similar between groups, and few significant differences were noted for nonpain outcomes

Pain. 2015 December ; 156(12): 2585–2594.

- **Global perceived effect** and **positive categorical outcome** over study course

	Pulsed radiofrequency group		Steroid injection group		Comparison of means
	No. of patients	**Overall mean (SD)**	**No. of patients**	**Overall mean (SD)**	***P***
Global perceived effect*					
6 wk	41	3.665 (1.344)	39	3.487 (1.222)	0.539†
3 mo	39	3.455 (1.372)	37	3.230 (1.234)	0.455†
6 mo	39	3.481 (1.353)	37	3.095 (1.241)	0.199†
	No. of patients	Number/Percentage	No. of patients	Number/Percentage	*P*
Positive categorical outcome‡					
6 wk	41	25/61	39	14/36	0.022§
3 mo	39	13/34	37	5/14	0.038§
6 mo	39	10/26	37	3/8	0.028§



Interventional Options for Refractory Migraines
Neuromodulation

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Peripheral Nerve Stimulation for Migraines

- PNS is effective for various forms of chronic, refractory headaches, including migraines
- Mechanism of action may involve activation of central endogenous pain modulation networks
  - **Popeney et al (2003)**
    - 25 chronic migraine patients; C1-C3 stimulation; 18 months follow-up
    - **88.7% improvement in headache quality** (MIDAS score)
    - Minimal residual disability in 15/25 patients

Current Pain and Headache Reports (2019) 23: 68

Peripheral Nerve Stimulation for Migraines

- Mechanism of action may involve activation of central endogenous pain modulation networks
  - **Matharu et al (2004) and Schedt et al (2007)**
    - **Occipital nerve stimulation**
    - Significant improvements in multitude of indices, including **headache frequency** (improvement of 25 fays from baseline of 89 days), **headache intensity** (2.4 points from baseline of 7.1 points), **MIDAS scores** (70 points from a baseline of 179 points), **HIT-6** (11 points from a baseline of 71 points), and **BDI-II scores** (8 points from a baseline of 20 points) at a mean follow-up of 19 months

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Peripheral Nerve Stimulation for Migraines

- Clinical trials of PNS on migraines:
  - **Saper et al (2011)**
    - First prospective trial on **occipital nerve stimulation**; multicenter RCT
    - 50% reduction in **headache frequency** and/or 3-point **intensity scale decrease** in 39% of 66 patients treated with PNS for 12 weeks
  - **Silberstein et al (2012)**
    - **Occipital nerve stimulation**; double-blind multicenter RCT, PRISM study
    - Mean decrease of 5.5 **migraine days/month** in 63 patients who received active stimulation and a decrease of 3.9 days/month in 62 patients who received sham stimulation at 12 weeks)
    - Significantly more patients achieved 30% **reduction in headaches** in PNS group

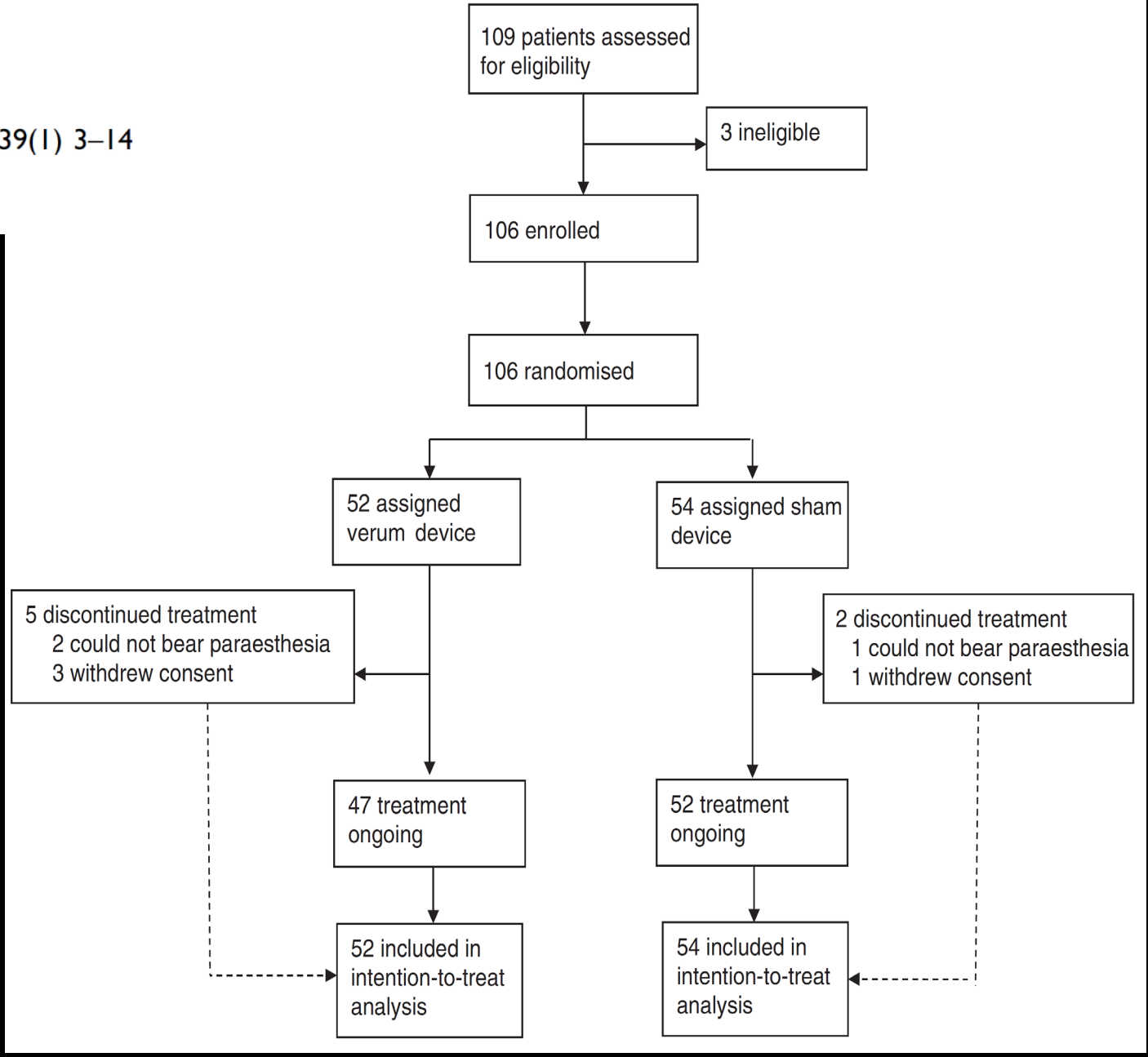
Current Pain and Headache Reports (2019) 23: 68

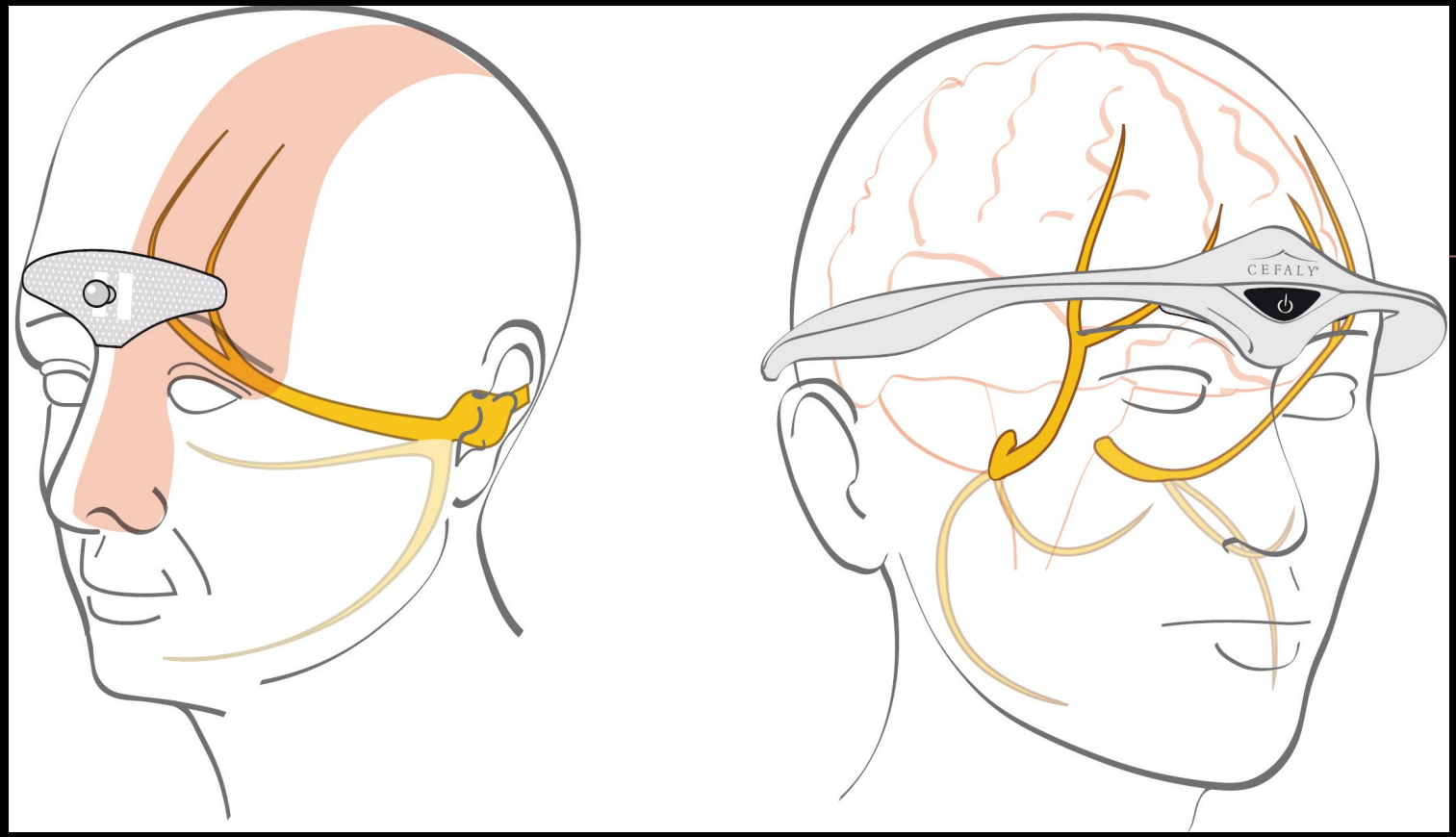
Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial

Cephalalgia 2019, Vol. 39(1) 3–14

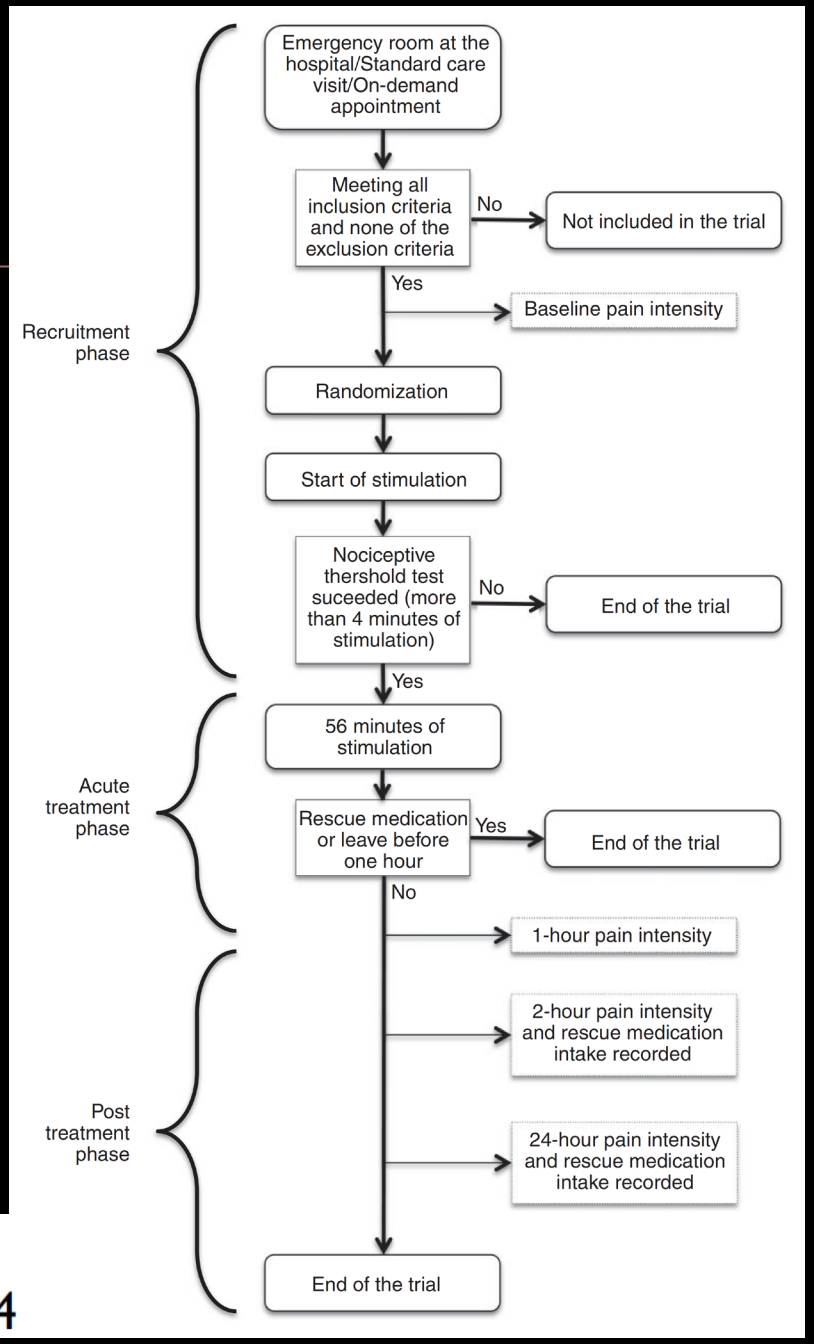
Denise E Chou[1], Marianna Shnayderman Yugrakh[1], Dana Winegarner[2], Vernon Rowe[2], Deena Kuruvilla[3] and Jean Schoenen[4]

- **Objective**: First randomized, double-blind, sham-controlled clinical trial evaluating the safety and efficacy of **1-hour external trigeminal nerve stimulation** for acute pain relief during **migraine** attacks via a sham-controlled trial





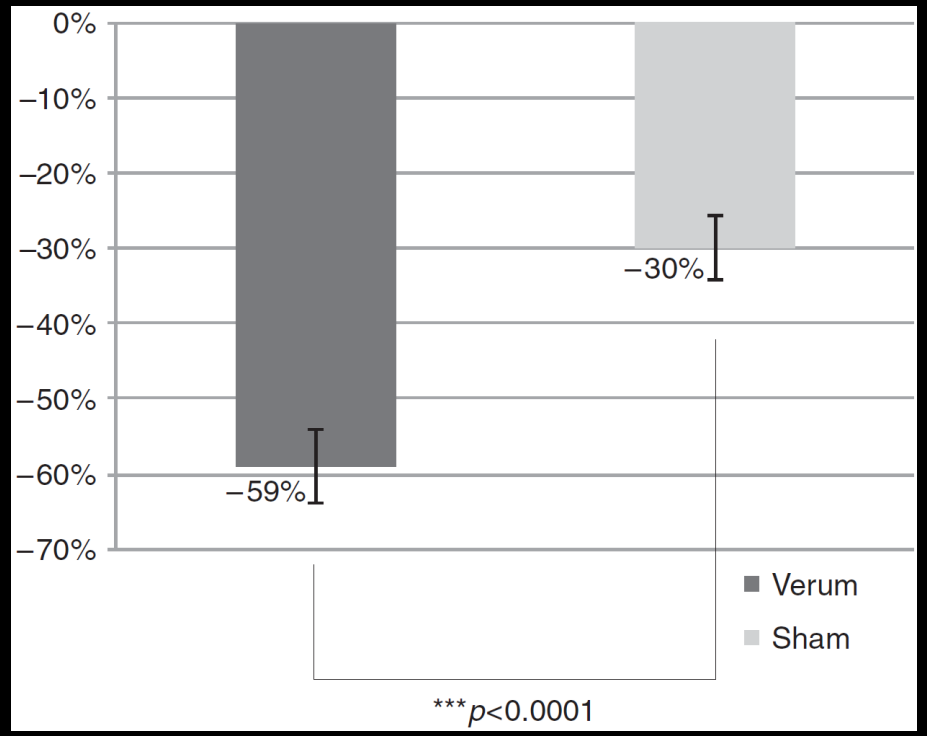
- Electrode positioning: (left) the electrode covers the supratrochlearis and supraorbitalis nerves, and (right) the neurostimulator device is placed on the forehead, and connected to the electrode



Cephalalgia
2019, Vol. 39(1) 3–14

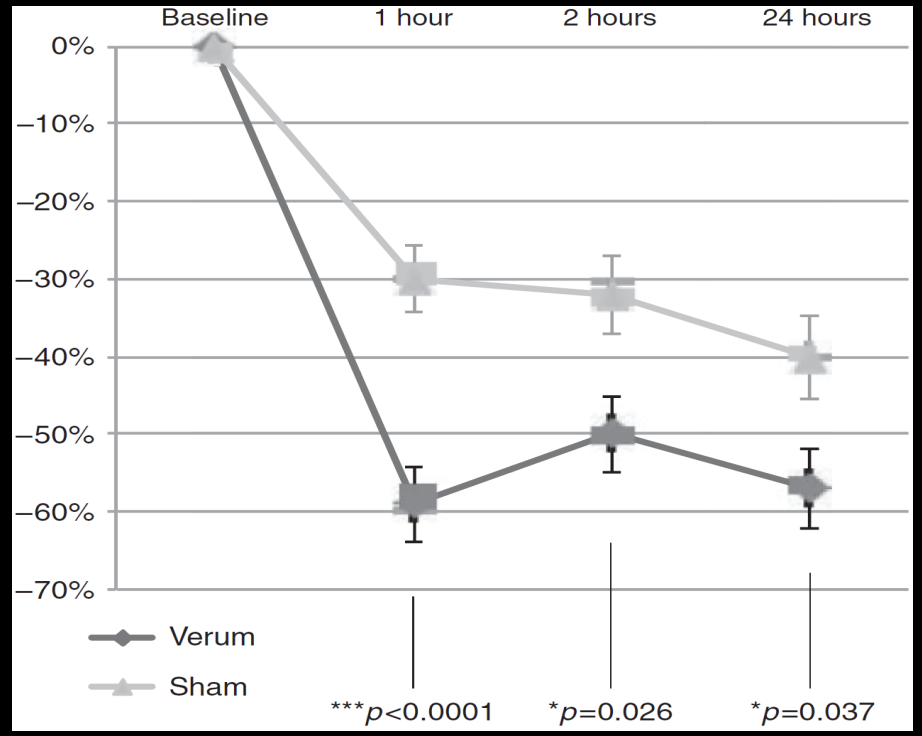
2019, Vol. 39(1) 3–14

- Use of e-TNS during a migraine attack provided a **significant reduction in mean headache pain intensity** at all time points compared to sham stimulation
- e-TNS was **safe and well-tolerated**



Relative change in pain intensity at 1 hour

Relative change in mean VAS scores at 1 hour, 2 hours, and 24 hours after treatment, compared to baseline



The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trails

Lihuan Lan[1†], Xiaoni Zhang[2†], Xiangpen Li[2†], Xiaoming Rong[2] and Ying Peng[2*]

The Journal of Headache and Pain (2017) 18:86

- Systematic review + meta-analysis of **5 RCTs with 313 migraine patients** on **transcranial magnetic stimulation**
  - **Results**
    - Single-pulse transcranial magnetic stimulation is **effective for the acute treatment of migraine** with aura after the first attack (p = 0.02)
    - The efficacy of TMS on **chronic migraine was not significant** (OR 2.93; 95% CI 0.71–12.15; p =0.14)

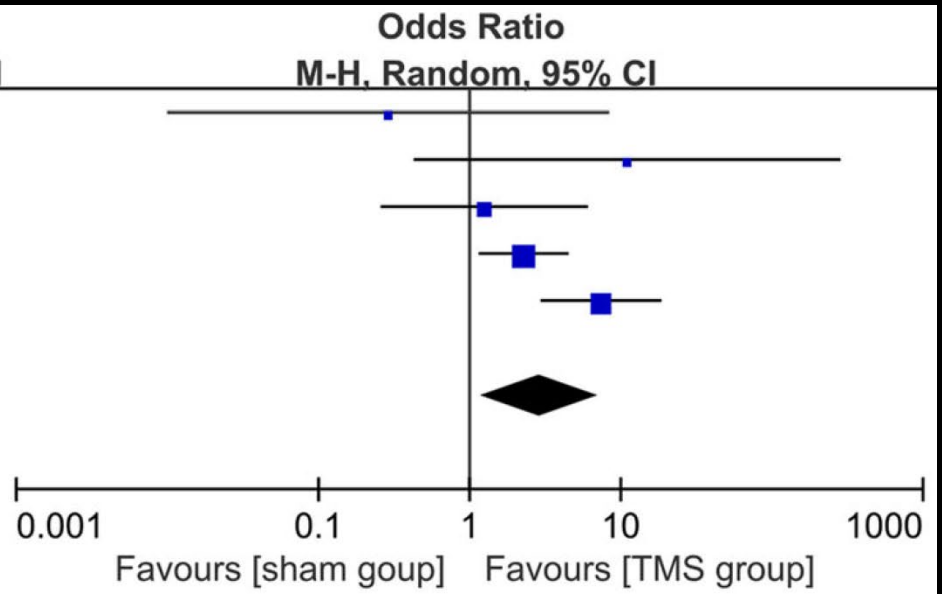
The Journal of Headache and Pain (2017) 18:86

- **Heterogeneity Among Studies and the Effect of TMS on Migraine**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adriana B Conforto 2013	0	7	1	7	6.1%	0.29 [0.01, 8.39]
Filippo Brighina 2004	3	6	0	5	6.5%	11.00 [0.43, 284.30]
Hatem S Shehata 2016	10	14	10	15	19.1%	1.25 [0.26, 6.07]
Richard B Lipton 2010	32	82	18	82	36.9%	2.28 [1.15, 4.52]
Usha K Misra 2013	37	47	16	48	31.4%	7.40 [2.95, 18.59]
Total (95% CI)		**156**		**157**	**100.0%**	**2.87 [1.17, 7.03]**
Total events	82		45			

Heterogeneity: $Tau^2 = 0.44$; $Chi^2 = 7.96$, df = 4 (P = 0.09); $I^2 = 50\%$

Test for overall effect: Z = 2.31 (P = 0.02)



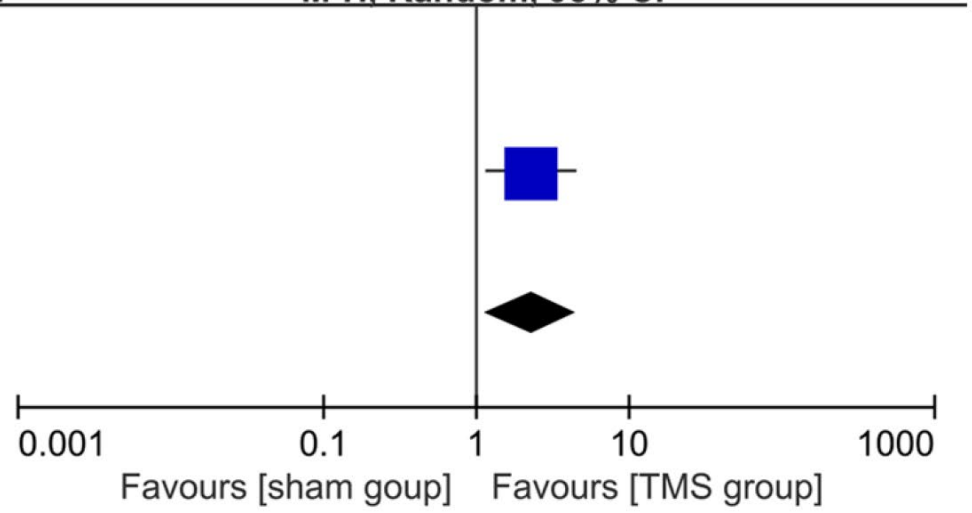
- For all studies, significant statistical heterogeneity was detected ($\chi 2 = 7.96$, p = 0 .09, I2 = 50%)
- Statistically significant effect of group (TMS group, control group) was found by analyzing all trials (OR 2.87; 95% CI 1.17–7.03; p = 0.02)

The Journal of Headache and Pain (2017) 18:86

- **The Effect of TMS on Migraine with Aura**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adriana B Conforto 2013	0	7	1	7	0.0%	0.29 [0.01, 8.39]
Filippo Brighina 2004	3	6	0	5	0.0%	11.00 [0.43, 284.30]
Hatem S Shehata 2016	10	14	10	15	0.0%	1.25 [0.26, 6.07]
Richard B Lipton 2010	32	82	18	82	100.0%	2.28 [1.15, 4.52]
Usha K Misra 2013	37	47	16	48	0.0%	7.40 [2.95, 18.59]
Total (95% CI)		**82**		**82**	**100.0%**	**2.28 [1.15, 4.52]**
Total events	32		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)



- 1 RCT (Lipton et al) assessed the efficacy of TMS on migraine with aura
- According to the study, more patients were pain-free at 2 hours post-treatment and there is significance that single-pulse transcranial magnetic stimulation is effective for the acute treatment of migraine with aura after the first attack (p = 0.02)

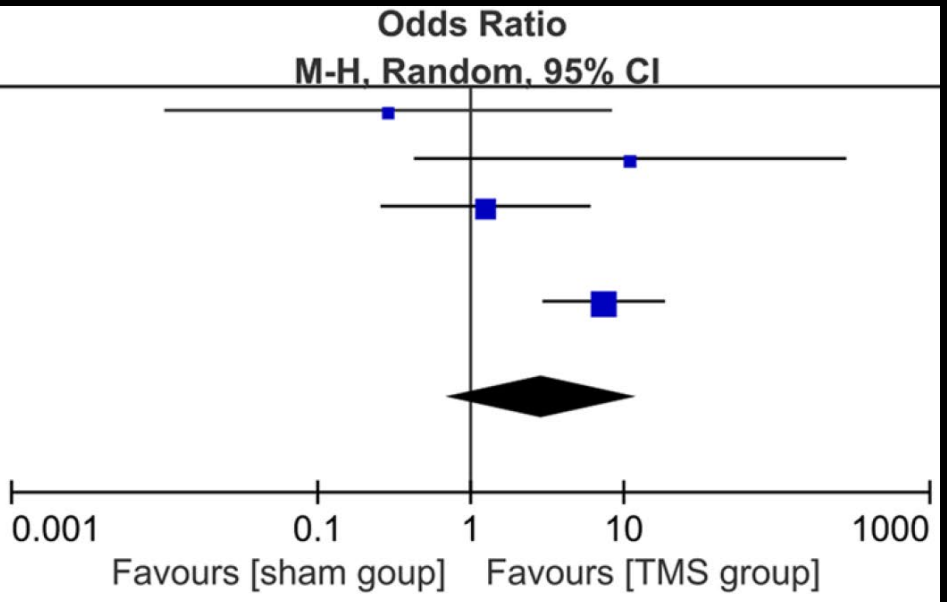
The Journal of Headache and Pain (2017) 18:86

- **The Effect of TMS on Chronic Migraine**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adriana B Conforto 2013	0	7	1	7	13.2%	0.29 [0.01, 8.39]
Filippo Brighina 2004	3	6	0	5	13.9%	11.00 [0.43, 284.30]
Hatem S Shehata 2016	10	14	10	15	31.2%	1.25 [0.26, 6.07]
Richard B Lipton 2010	32	82	18	82	0.0%	2.28 [1.15, 4.52]
Usha K Misra 2013	37	47	16	48	41.8%	7.40 [2.95, 18.59]
Total (95% CI)		**74**		**75**	**100.0%**	**2.93 [0.71, 12.15]**
Total events	50		27			

Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 6.49$, df = 3 (P = 0.09); $I^2 = 54\%$

Test for overall effect: Z = 1.48 (P = 0.14)



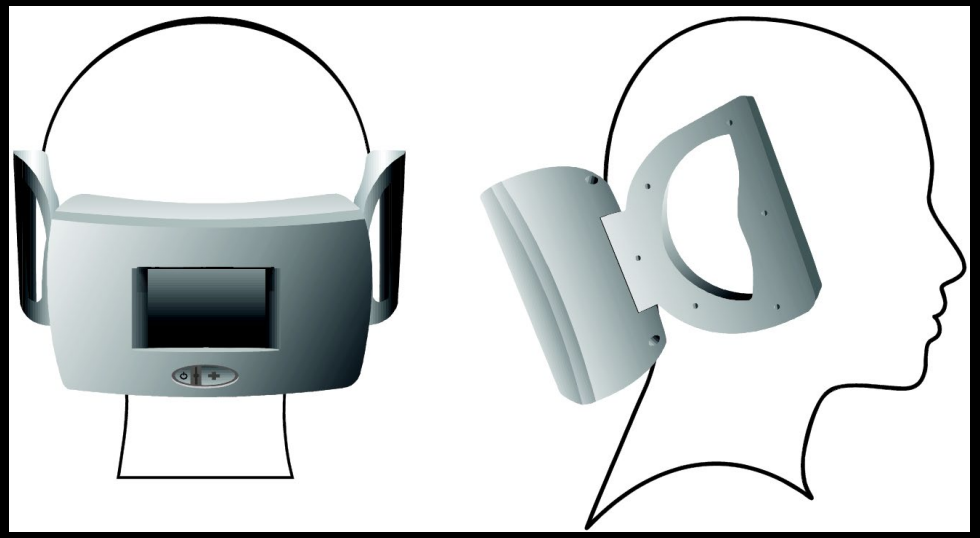
- 4 RCTs researched the effect of TMS on chronic migraine
- Statistical heterogeneity was detected among the trails ($\chi 2 = 6.49$, p = 0 .09, I2 = 54%)
- Efficacy of TMS on chronic migraine was not significant (OR 2.93; 95% CI 0.71 – 12.15; p = 0.14)

Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program

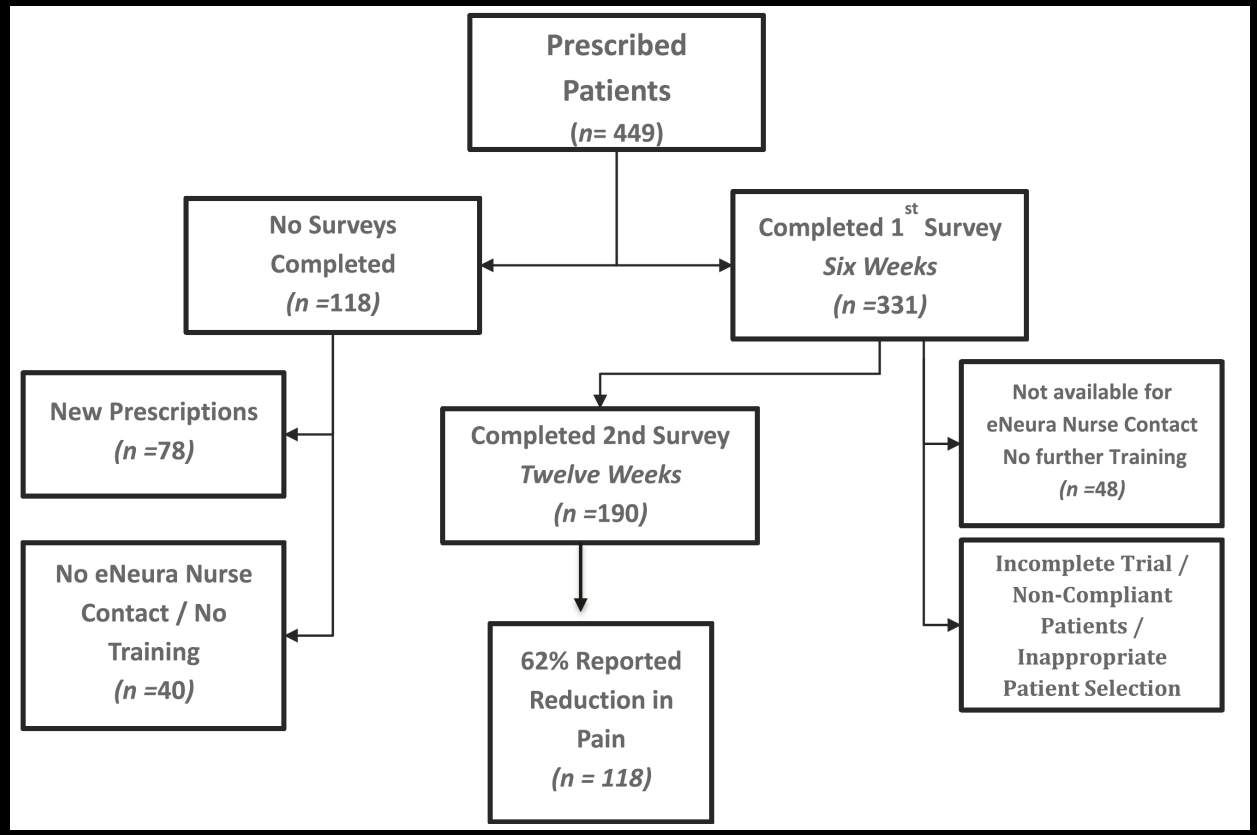
J Headache Pain. 2015;16:535.

Ria Bhola[1], Evelyn Kinsella[1], Nicola Giffin[2], Sue Lipscombe[3], Fayyaz Ahmed[4], Mark Weatherall[5] and Peter J Goadsby[6,7*]

- Objective: evaluate acute migraine patient response to **single-pulse transcranial magnetic stimulation (sTMS)** in the setting of routine clinical practice



Position of device for treatment



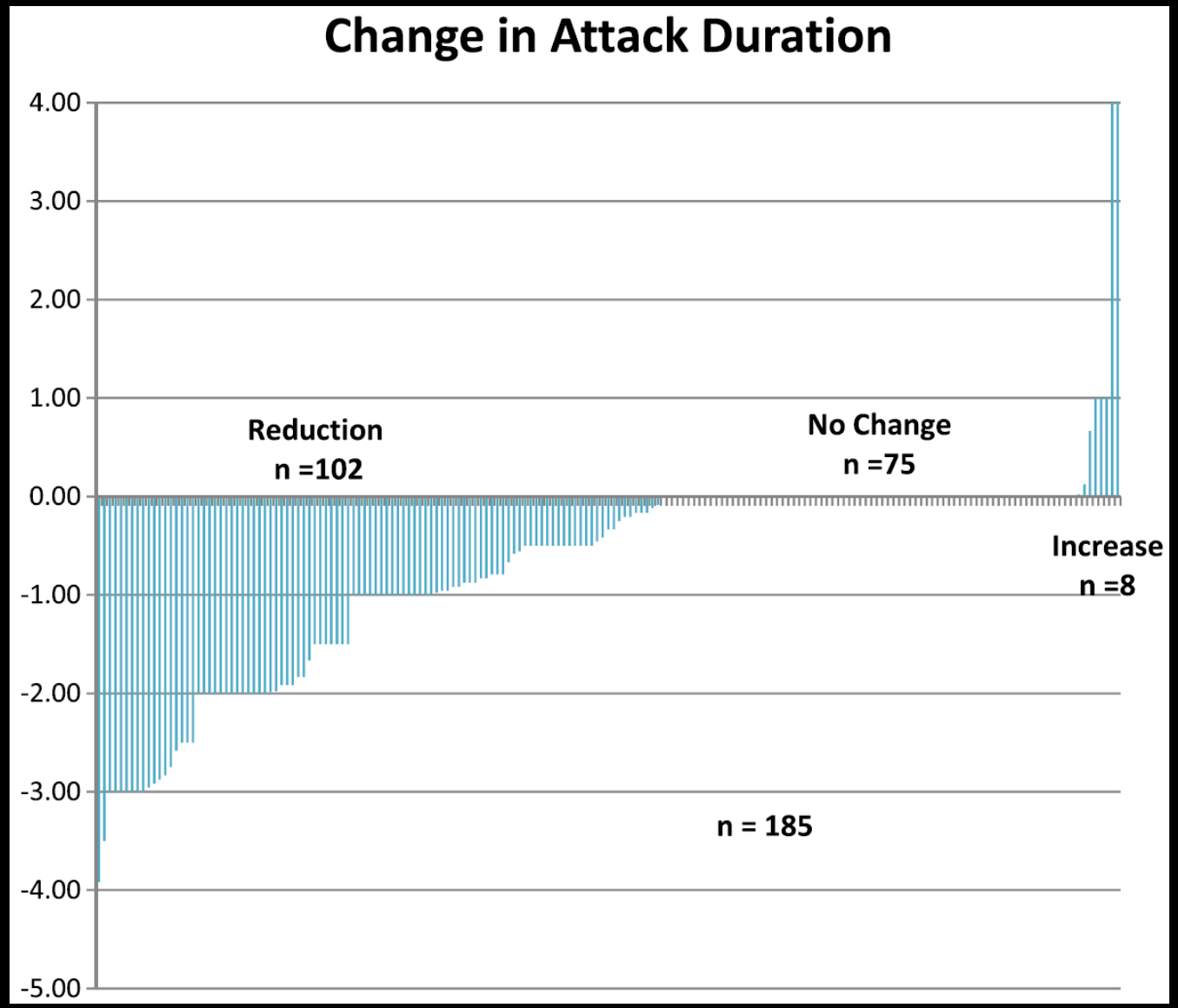
J Headache Pain. 2015;16:535.

- Results after 3 months follow-up:
  - **62%** (n = 190; episodic, n = 59; chronic, n = 131) **reported pain relief**
  - Relief reported of associated features: nausea 52%, photophobia 55%, and phonophobia 53%

Migraine days/month	Baseline	6 weeks	12 weeks
<5	8	11	27
5–9	19	35	33
10–14	35	42	45
15–20	56	36	32
21–25	14	12	9
26–30	58	52	44
Pain severity[a]	Baseline	6 weeks	12 weeks
0	0	3	2
1–3	0	44	63
4–6	32	85	75
7–9	140	54	47
10	18	4	3
Duration in days	Baseline	6 weeks	12 weeks
<1	34	66	84
1	55	55	48
2	34	30	27
3	41	24	20
4	19	7	3
>4	2	2	3

J Headache Pain. 2015;16:535.

- Change in attack duration plotted by patient. While 102 patients had a reduction, 75 had no change and 8 had an increase

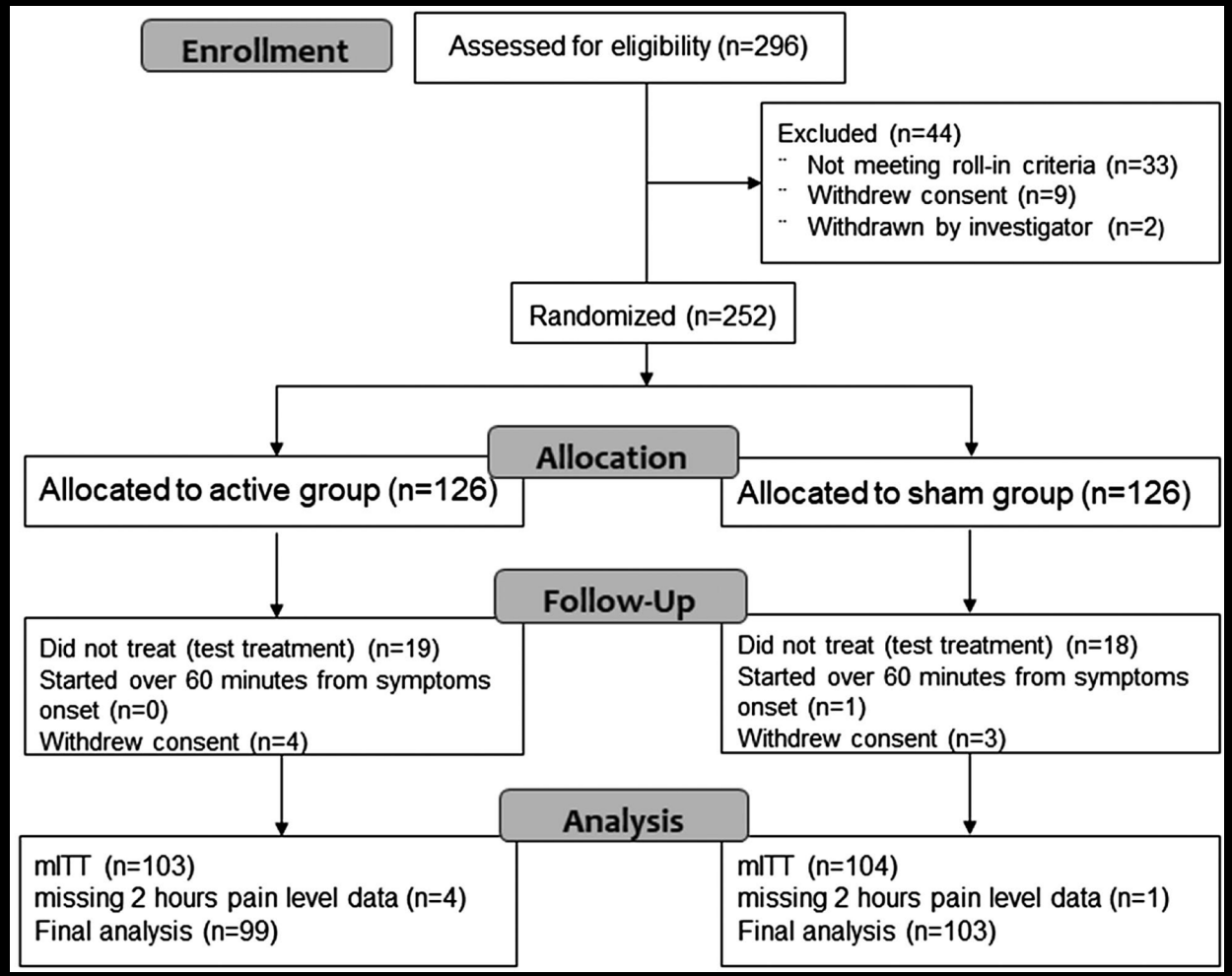


Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Headache 2019;59:1240-1252

David Yarnitsky, MD; David W. Dodick, MD; Brian M. Grosberg, MD; Rami Burstein, PhD; Alon Ironi, MSEE; Dagan Harris, PhD; Tamar Lin, PhD; Stephen D. Silberstein, MD

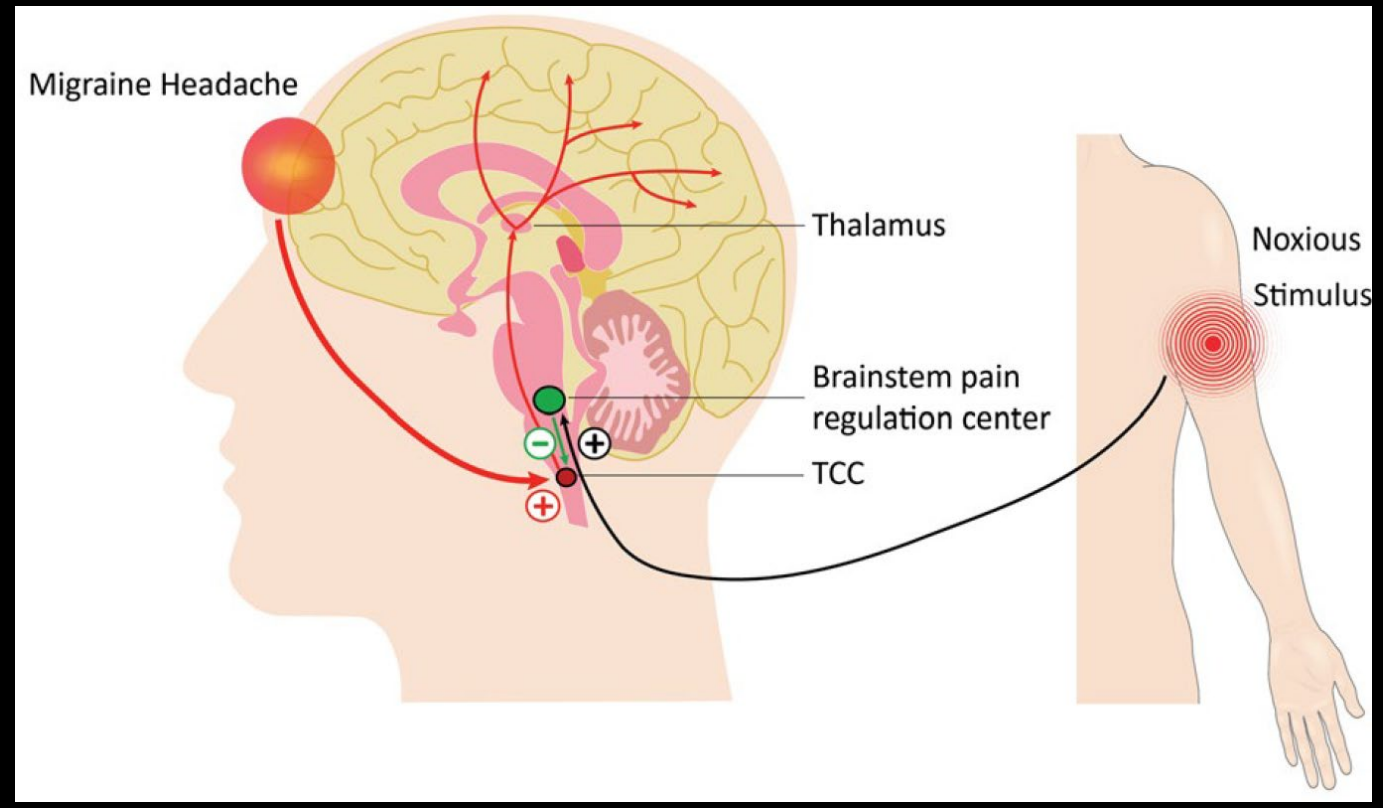
- Objective: assess the **safety and efficacy of a remote electrical neuromodulation (REN)** device for acute migraine; **n = 252 patients** with 2-8 migraines/month
- REN stimulates upper arm peripheral nerves to induce conditioned pain modulation – an endogenous analgesic mechanism in which conditioning stimulation inhibits pain in remote body regions



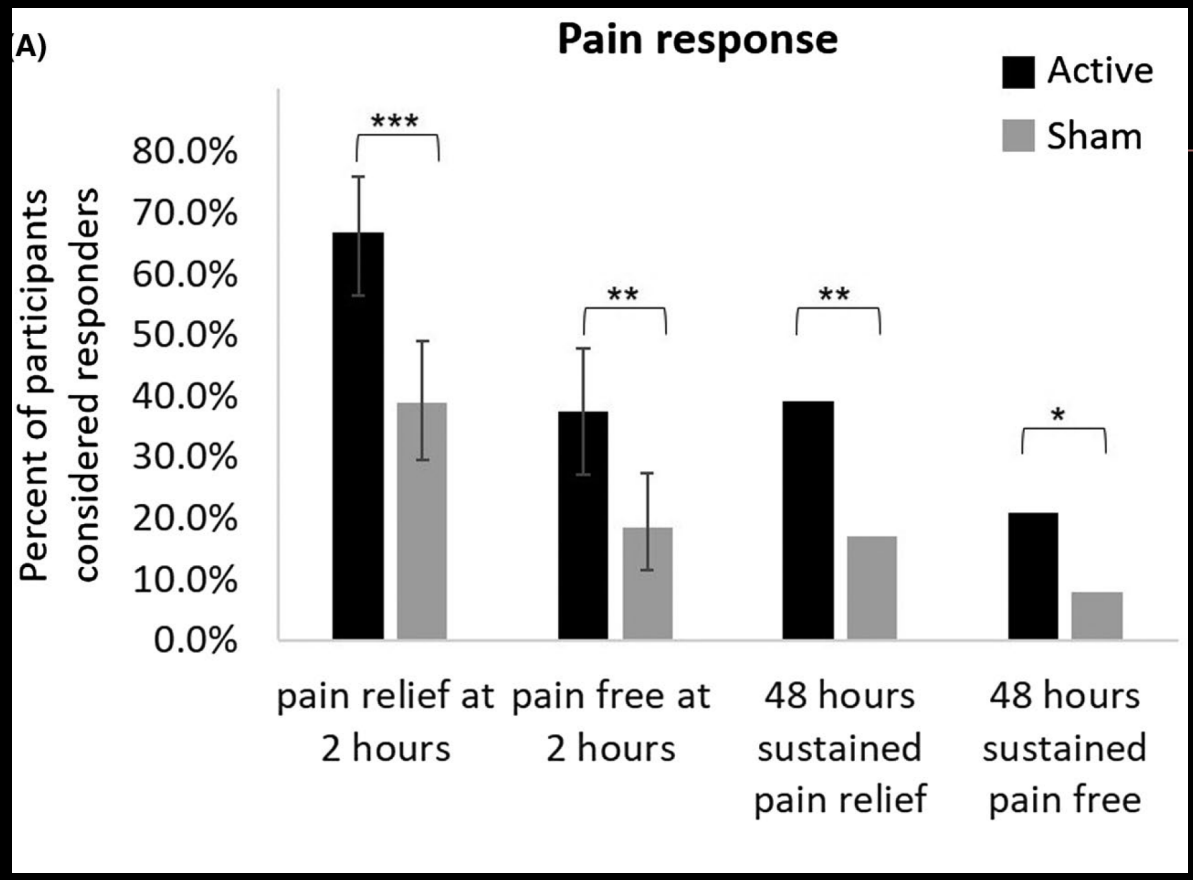
Headache 2019;59:1240-1252

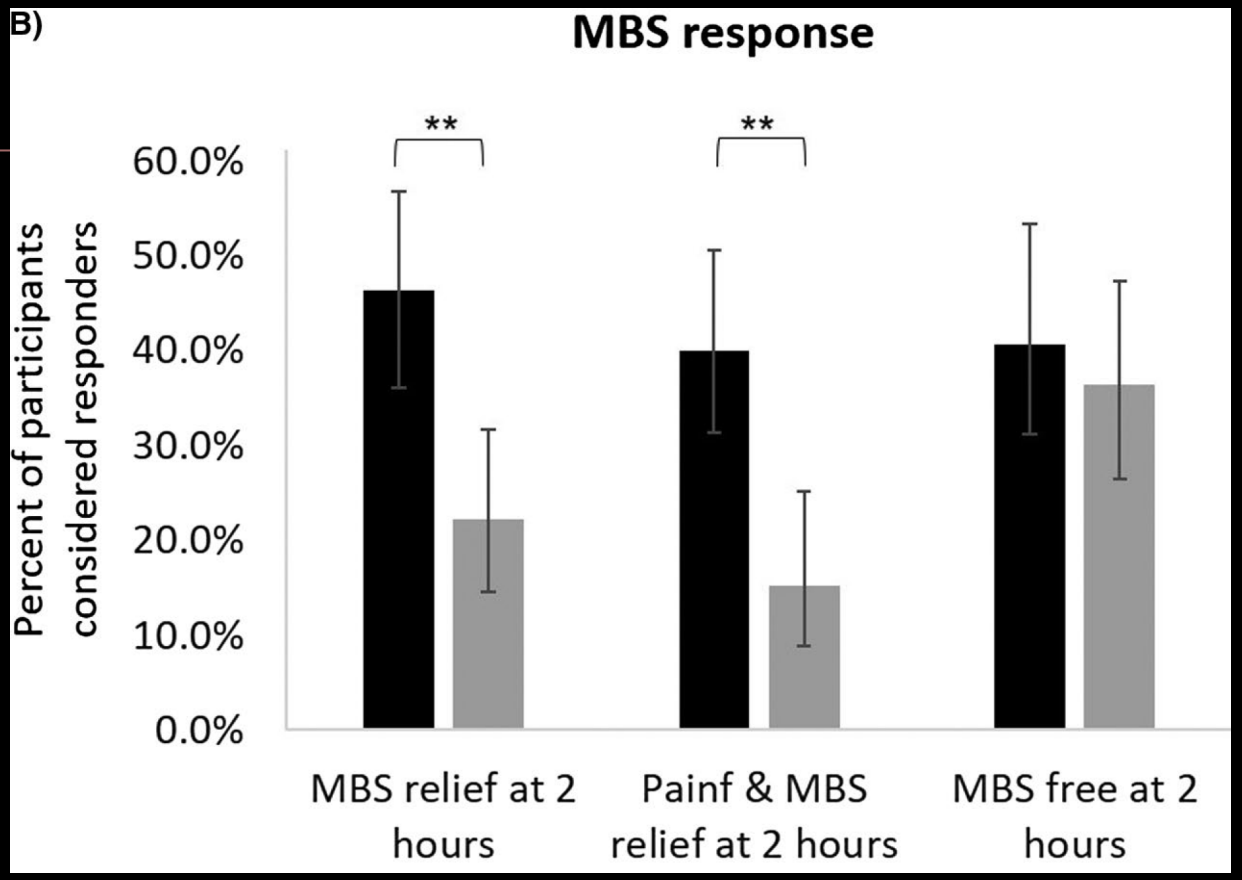
- **Remote electrical neuromodulation (REN)**

- Smartphone-controlled wireless device was applied for 30-45 minutes on the upper arm within 1 hour of attack onset; electrical stimulation was at a perceptible but non-painful intensity level



Headache 2019;59:1240-1252





- (A) Pain response at 2 and 48 hours post-treatment
- (B) MBS response at 2 hours post-treatment
  - The error bars represent 95% confidence intervals
  - ***P < .001, **P < .005, *P < .05. MBS = most bothersome symptom

Headache 2019;59:1240-1252

- Results:
  - **Active stimulation was more effective than sham stimulation** in achieving pain relief, pain-free, and MBS relief at 2 hours post-treatment
  - Pain relief and pain-free superiority of the active treatment was sustained at 48 hours
  - Incidence of device-related adverse events was low and similar between treatment groups (4.8% vs 2.4%, P = .499)

	Active Group (N = 99)	Sham Group (N = 103)	*P* Value
Pain relief at 2 hours post-treatment†	66.7% (66/99)	38.8% (40/103)	<.001
Pain-free at 2 hours post-treatment‡	37.4% (37/99)	18.4% (19/103)	.003
MBS relief at 2 hours post-treatment§	46.3% (44/95)	22.2% (22/99)	<.001
Pain relief & MBS relief at 2 hours post-treatment	40.0% (38/95)	15.2% (15/99)	<.001
MBS free at 2 hours post-treatment	40.7% (33/81)	36.4% (32/88)	.55
Sustained pain-free response at 48 hours post-treatment	20.7% (18/87)	7.9% (7/89)	.014
Sustained pain relief response at 48 hours post-treatment	39.1% (34/87)	16.9% (15/89)	.001
Within-subject consistency§	62.6% (62/99)	45.6% (47/103)	.015
Pain relief at 2 hours as a function of the baseline pain level			.84††
Mild	54.3% (19/35)	30.2% (13/43)	
Moderate	77.2% (44/57)	50.0% (23/46)	
Severe	42.9% (3/7)	28.6% (4/14)	

Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications

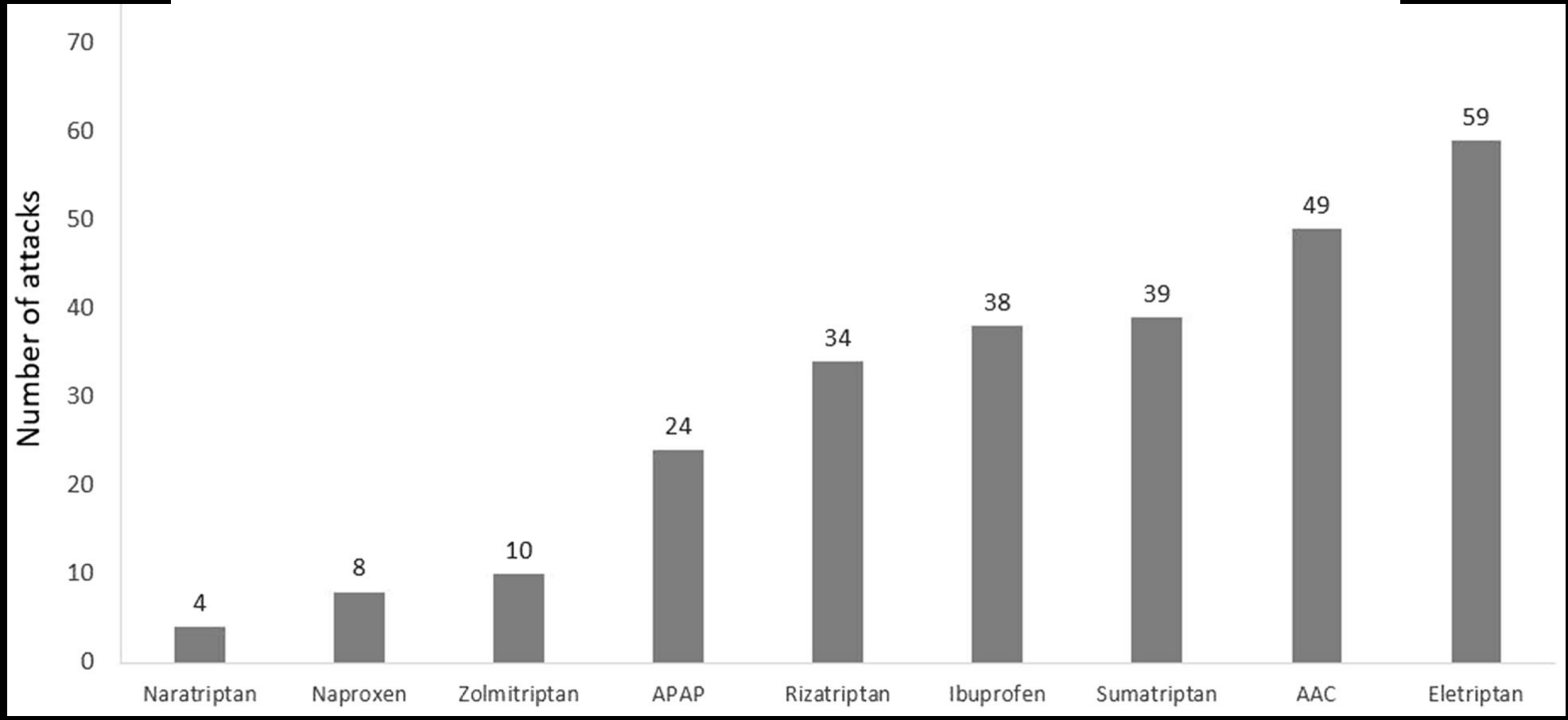
The Journal of Headache and Pain (2019) 20:83

Alan M. Rapoport[1*], Jo H. Bonner[2], Tamar Lin[3], Dagan Harris[3], Yaron Gruper[3], Alon Ironi[3] and Robert P. Cowan[4]

- Efficacy of **REN** was compared to the efficacy of usual care or pharmacological treatments in a post-hoc analysis on **99 participants** with migraine from a randomized, double-blind, sham-controlled, study

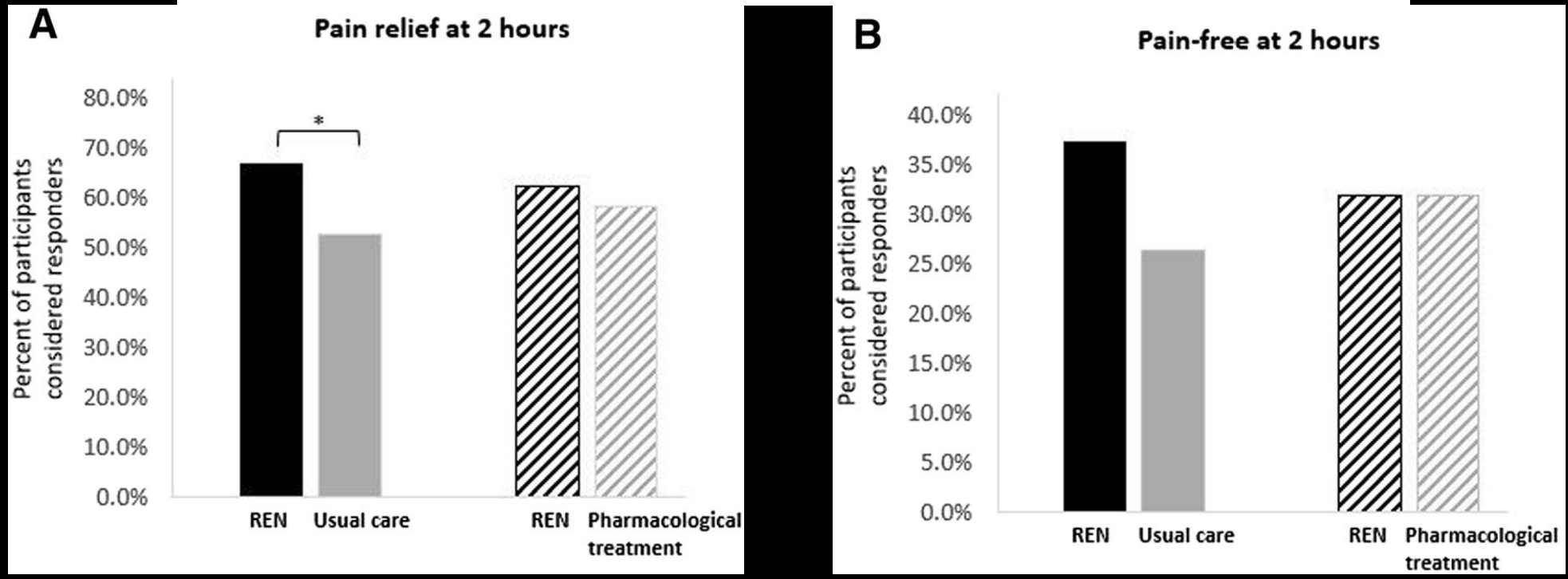
- Results
  - **2 hours post-treatment: pain relief was achieved in 66.7%** of the participants using REN vs 52.5% participants with usual care ($p < 0.05$)
  - Pain relief at 2 hours in at least 1 of 2 attacks was achieved by 84.4% of participants vs 68.9% in usual care ($p < 0.05$). REN and usual care were similarly effective for pain-free status at 2 hours
  - **Non-inferiority of REN compared with acute pharmacological treatments** and its non-dependency on preventive medication use

The Journal of Headache and Pain (2019) 20:83



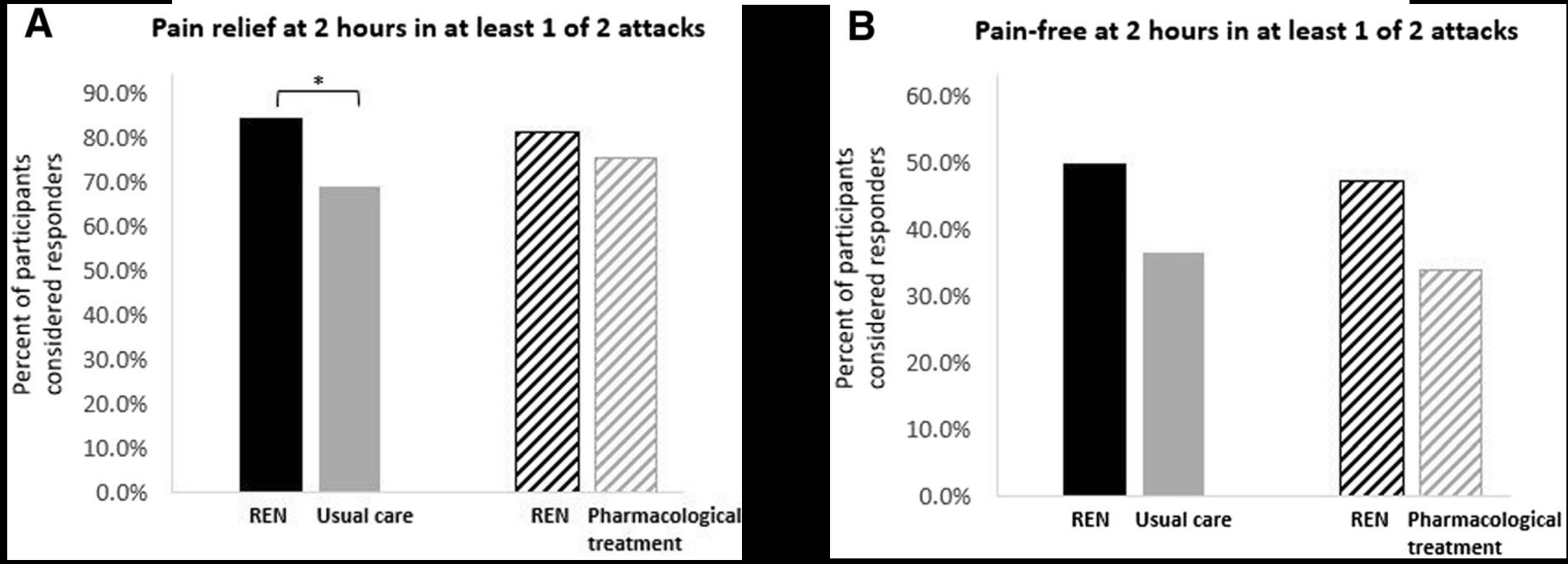
- Number of participants using different types of acute pharmacological treatments in their first reported attack in the run-in phase
- AAC: aspirin, acetaminophen, and caffeine; APAP: acetaminophen

The Journal of Headache and Pain (2019) 20:83



- **Efficacy comparison of pain responses in a single attack**
- A. Pain relief at 2 hours post-treatment of REN (solid black and diagonal black) compared with usual care (solid gray) and pharmacological treatment (diagonal gray)
- B. Pain-free at 2 hours post-treatment of REN (solid black and diagonal black) compared with usual care (solid gray) and pharmacological treatment (diagonal gray)
- *$p < 0.05$

The Journal of Headache and Pain (2019) 20:83



- **Efficacy comparison of pain responses in at least 1 of 2 attacks**
- A. **Pain relief at 2 hours** post-treatment **in at least 1 of 2 attacks** following REN treatment (solid black and diagonal black) compared with responses usual care (solid gray) and pharmacological treatment (diagonal gray)
- B. **Pain-free at 2 hours** post-treatment **in at least 1 of 2 attacks** following REN treatment (solid black and diagonal black) compared with usual care (solid gray) and pharmacological treatment (diagonal gray). *$p < 0.05$

Interventional Options for Cervicogenic Headaches

Occipital Neuralgia and Cervicogenic Headache: Diagnosis and Management

Rebecca Barmherzig [1,2] · William Kingston [1]

Current Neurology and Neuroscience Reports (2019) 19: 20

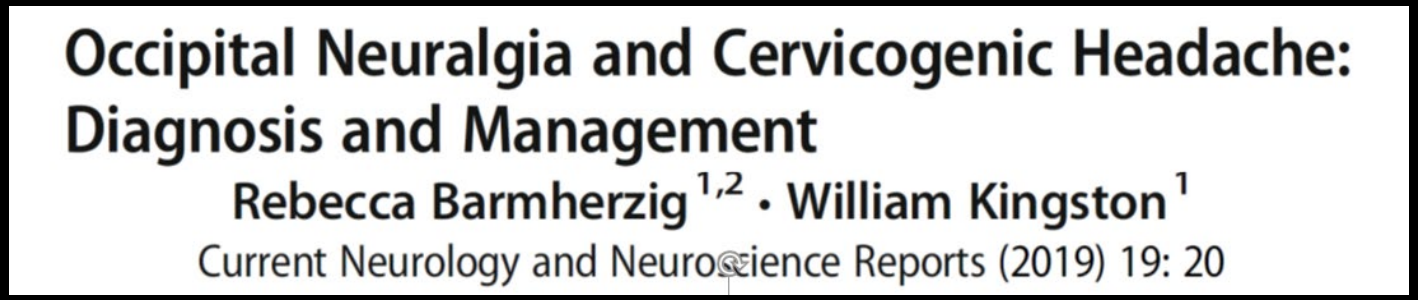
- **Nonpharmacologic strategies** for cervicogenic headaches
  - Massage, cool compresses, cranio-cervical exercises, physiotherapy to improve posture, spinal manipulation therapy, transcutaneous electrical nerve stimulation
- **Pharmacologic strategies** for cervicogenic headaches
  - NSAIDs, tricyclic antidepressants such as amitriptyline, muscle relaxants such as baclofen, and anticonvulsants such as gabapentin or carbamazepine
  - Opioids are not used due to lack of evidence for benefit and risk of side effects and dependence
  - Drugs targeting proinflammatory mediators such as cytokines and TNF-a are currently being investigated
  - Botulinum toxin A has been used in the treatment of several primary headache disorders, mainly migraines. Occipital nerve block injections with botulinum toxin A have been studied in small case series

Occipital Neuralgia and Cervicogenic Headache: Diagnosis and Management

Rebecca Barmherzig [1,2] · William Kingston [1]

Current Neurology and Neuroscience Reports (2019) 19: 20

- **Interventional strategies** for cervicogenic headaches:
  - Anesthetic block of the greater and/or lesser occipital nerves are used both diagnostically and therapeutically; limited evidence due to uncontrolled studies
  - Occipital nerve blocks with or without corticosteroids yield transient benefit in most, with 15%–36% sustaining extended relief for several months
  - Facet block or anesthetic block of the upper cervical nerves with corticosteroid has also been used as a therapeutic approach
  - Intra-articular corticosteroid injections may be beneficial in reducing short-term pain, but may have less benefit long-term



- **Minimally invasive surgical strategies** for cervicogenic headaches:
  - For patients failing above interventions, options include neuromodulation with subcutaneous occipital nerve stimulation (ONS), or pulsed radiofrequency therapy
- **Invasive surgical strategies** for cervicogenic headaches:
  - Invasive surgical options have mixed results, should be weight against possibility for poor longevity and frequent, significant side effects
  - Include neurolysis, posterior partial rhizotomy, and dorsal root entry zone lesioning

Treatment of Cervicogenic Headache with Cervical Epidural Steroid Injection

Eugene Wang · Dajie Wang Curr Pain Headache Rep (2014) 18:442

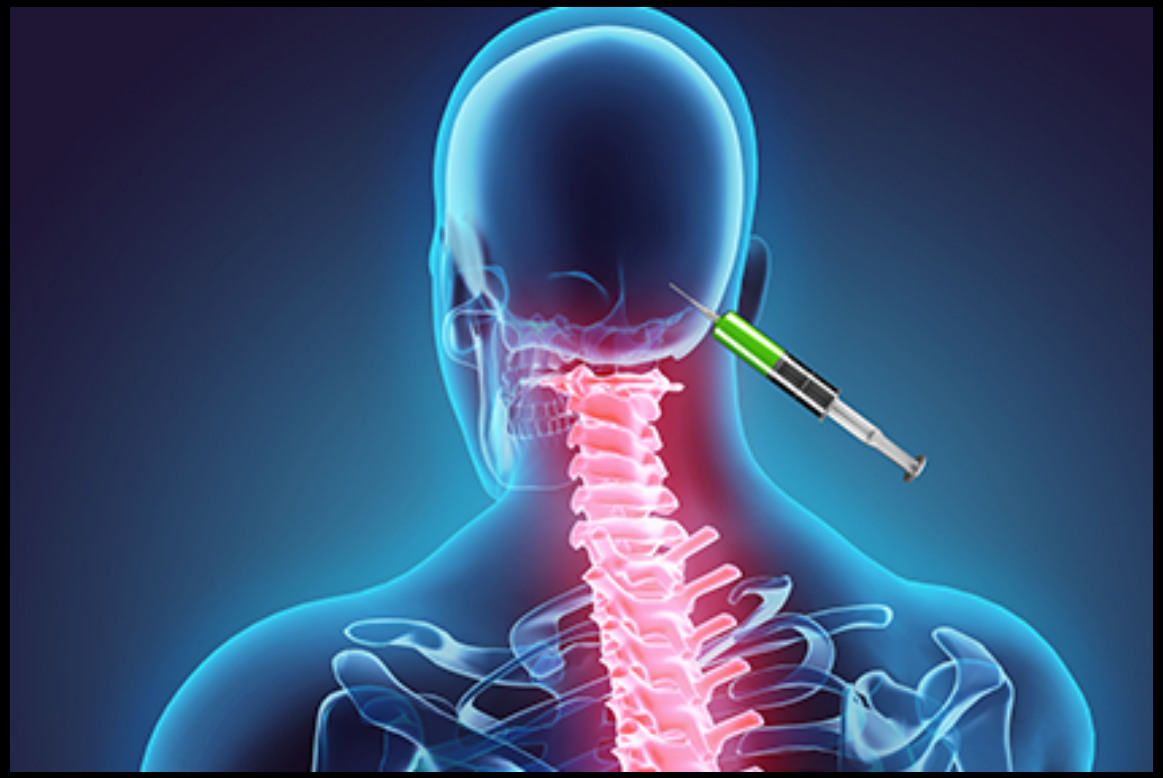
- Review of studies using **cervical epidural steroid injection (CESI)** in the treatment of cervicogenic headache (CGH)

Eur Rev Med Pharmacol Sci. Jan-Feb 1998;2(1):31-6.

- Martelleti et al: prospective case-control study **in 9 CGH patients** and 6 tension-type headache controls
- Results: sharp **decrease in Numerical Intensity Scale and Drug Consumption Index observed in the CGH group treated with CESI** compared with the control group, statistically significant short-term (12 hours) and medium-term (4weeks) improvement

Chin Med J (Engl). 2009 Feb 20;122(4):427-30.

- He et al: retrospective analysis of **37 CGH patients** with CESI
- Results: **significant decrease at 3 and 6 months post-infusion in number of days with mild to moderate pain, occurrence of severe pain, and NSAID usage**. No significant differences observed at 12 months post-infusion



Interventional Options for Cervicogenic Headaches
Nerve Blocks

Efficacy of the Greater Occipital Nerve Block for Cervicogenic Headache: Comparing Classical and Subcompartmental Techniques

© 2014 World Institute of Pain, 1530-7085/14/$15.00
Pain Practice, Volume 15, Issue 7, 2015 654–661

Gabriela R. Lauretti, MD, PhD, FIPP; Selma W. R. O. Corrêa, MD, Msc; Anita L. Mattos, MD, PhD

- Aim: compare the efficacy of **greater occipital nerve (GON) block** using the classical technique and **different volumes of injectate** with the subcompartmental technique
- Methods: **n = 30** CGH patients
  - All patients were submitted to the GON block by the classical technique with 10 mg dexamethasone, plus 40 mg lidocaine (5 mL volume)
  - Patients were randomly allocated into 1 of 3 groups (n = 10) when pain VAS was > 3 cm

	Classic Technique	Sub Occipital Compartment Technique
Group 5	5 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 2 mL saline	5 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 0.5 mL saline + 1.5 mL non-ionic iodine contrast
Group 10	5 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 2 mL saline	10 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 3.5 mL saline + 3.5 mL non-ionic iodine contrast
Group 15	5 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 2 mL saline	15 mL: 10 mg dexamethasone (1 mL) + 2 mL 2% lidocaine + 5 mL saline + 7 mL non-ionic iodine contrast

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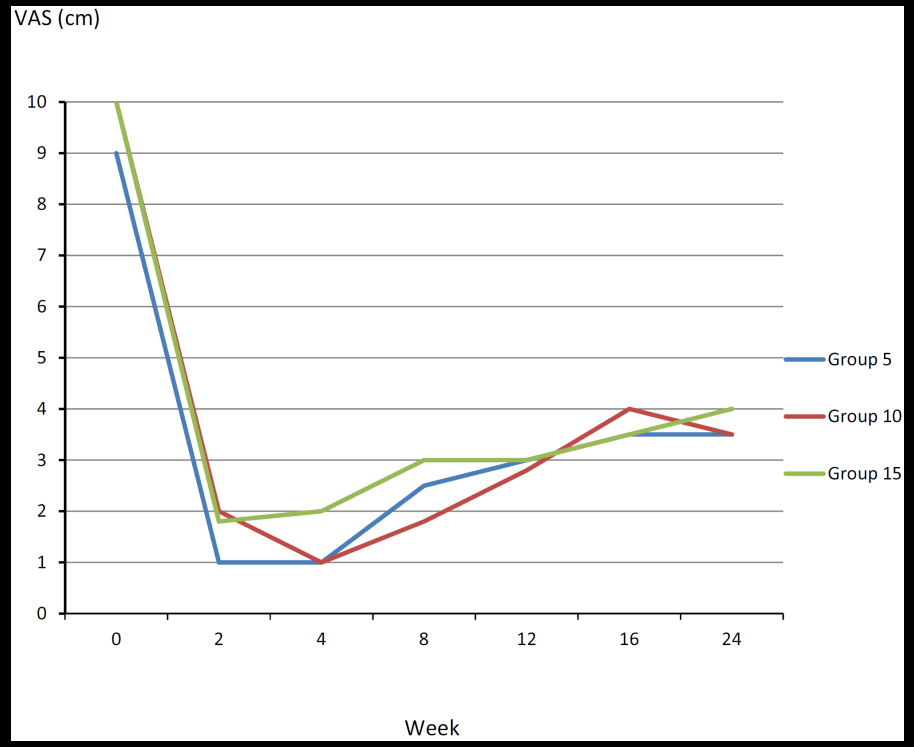
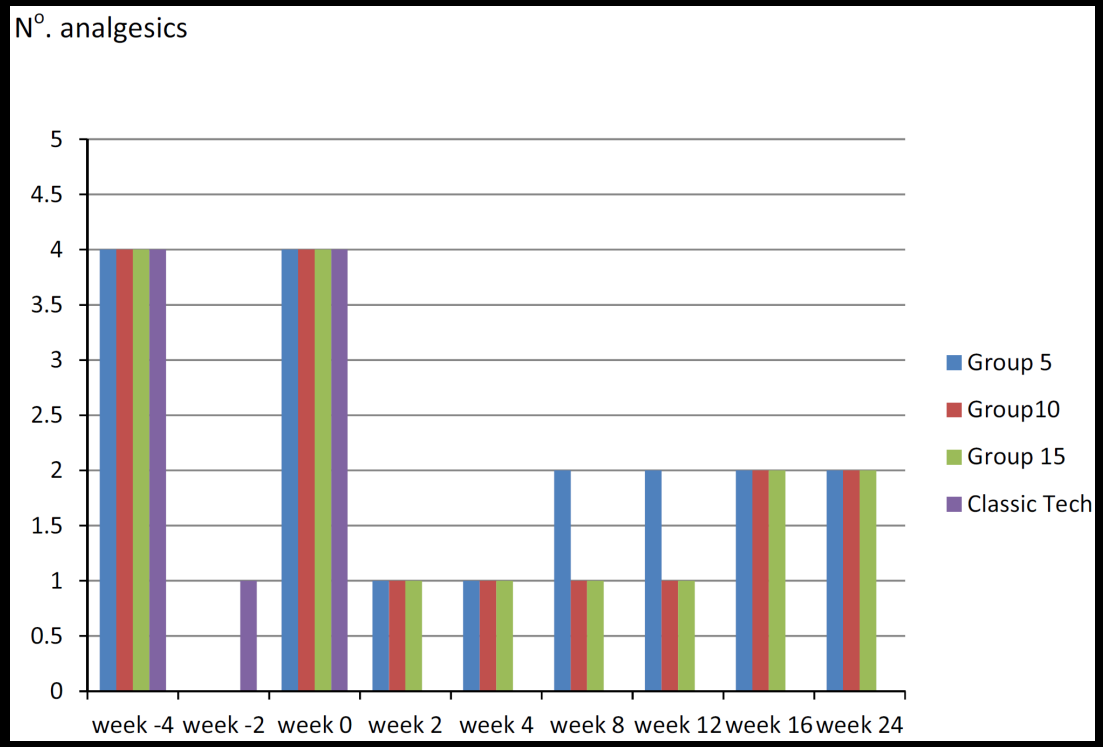
Pain Practice, Volume 15, Issue 7, 2015 654–661

- Results: While the classical technique for **GON block resulted in only 2 weeks of analgesia**, the **subcompartmental technique resulted in at least 24 weeks** of analgesia, being 5 mL volume sufficient for the performance of the block under fluoroscopy.



Weekly VAS evolution for the study groups



Number of daily rescue analgesics

PainWeek

Interventional Options for Cervicogenic Headaches
Radiofrequency

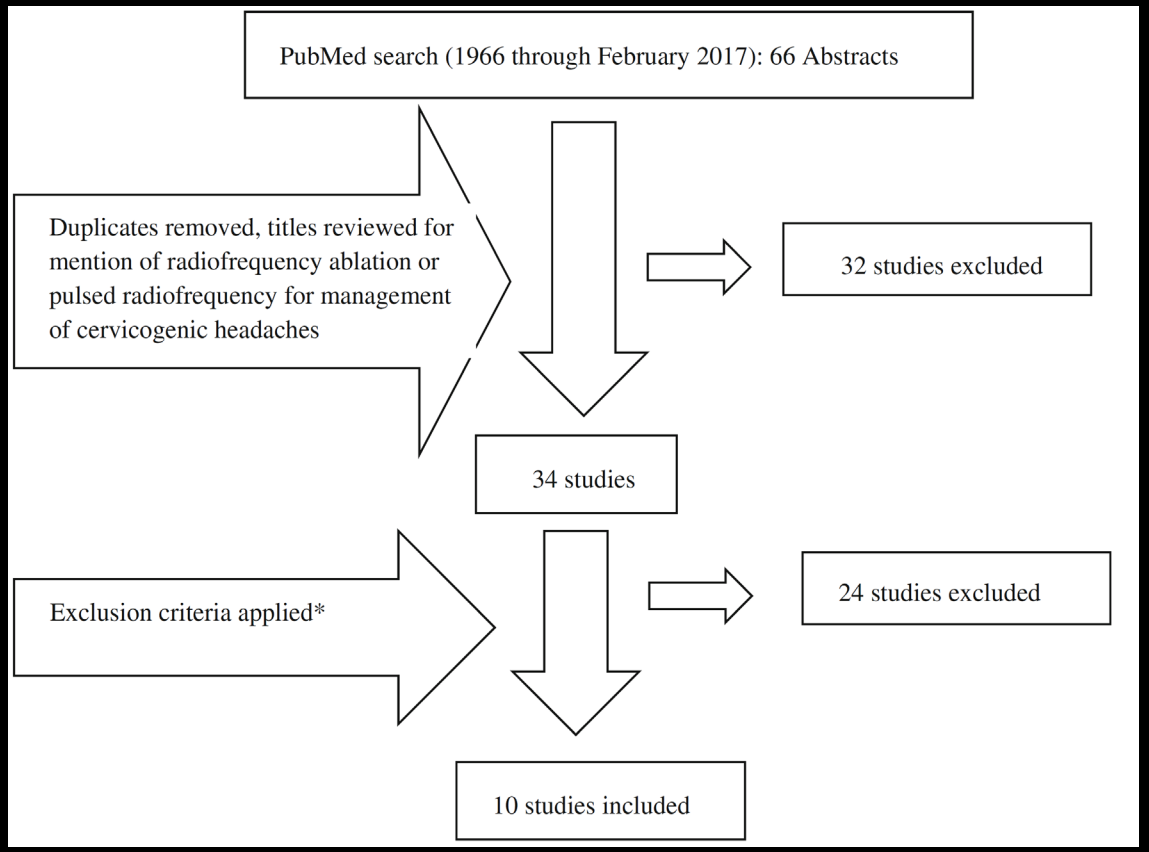
PainWeek®

Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headaches

Ravi K. Grandhi[1] · Alan David Kaye[2] · Alaa Abd-Elsayed[3]

Current Pain and Headache Reports (2018) 22: 18

- Systematic review including **10 studies** on the use of **radiofrequency ablation and pulse radiofrequency** for the management of refractory cervicogenic headaches
- Conclusions:
  - **RFA and PRFA provide very limited benefit** in the management of cervicogenic headaches
  - More high-quality RCT and/or strong non-RCTs to support the use of these techniques, despite numerous case reports which have demonstrated benefit



Current Pain and Headache Reports (2018) 22: 18

- Case studies highlighting impacting of RFA or PRF

Case reports	Patients	Conclusion
Sjaastad et al. 1995 [32]	7	RFA of the planum nuchale can treat CHA.
Van Zundert et al. 2003 [33]	18	> 50% pain relief was achieved in > 70% of patients at 8 weeks. However, only 33% of patients had pain relief at 1 year.
Zhang et al. 2011 [34]	2	PRF is effective in the treatment of CHA originating from the C2 nerve.
Bovaira et al. 2013 [35]	3	RF is effective in management of CHA. However, it is often transient.
Kim et al. 2013 [36]	2	PRF is effective in patients with occipital headache and posterior neck pain.
Giblin et al. 2014 [37]	1	RFA can be used to manage CHA+ Right third occipital nerve headache symptoms.
Gorelov et al. 2016 [38]	1	RFA can be used to manage CHA.
Odonkor et al. 2017 [39]	1	RFA showed effective pain management in a patient at 2, 4, 8, and 12 weeks with maximum efficacy at 12 weeks.

Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headache

Vittal R. Nagar, MD, PhD[1], Pravardhan Birthi, MD[2], Jay S. Grider, DO, PhD[3], and Amit Asopa, MD, FRCA[4]

Pain Physician 2015; 18:109-130

- Systematic review including 9 studies to investigate the **clinical utility of radiofrequency (RF) neurotomy, and pulsed radiofrequency (PRF) ablation** for the management of cervicogenic headache
- Results:
  - There were **5 non-randomized**, among them 4/5 were of moderate quality, **3/5 showed RF ablation and 1/5 showed PRF as an effective intervention** for cervicogenic headache
  - There were **4 randomized trials** among them 2/4 were of high quality, 3/4 investigated RF ablation as an intervention, 1/4 investigated PRF ablation as an intervention, and **none of the randomized studies showed strong evidence for RF and PRF ablation as an effective intervention** for cervicogenic headaches

Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headache

Vittal R. Nagar, MD, PhD[1], Pravardhan Birthi, MD[2], Jay S. Grider, DO, PhD[3], and Amit Asopa, MD, FRCA[4]

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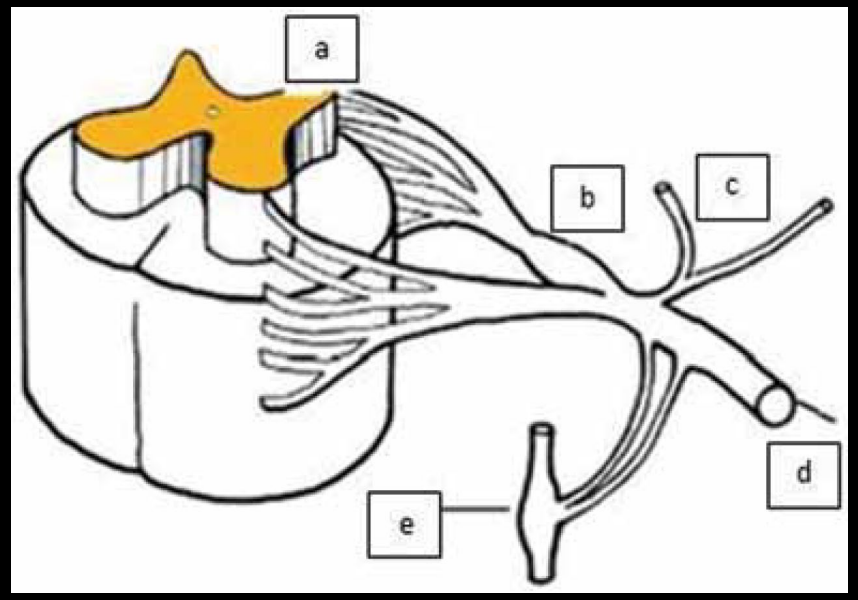
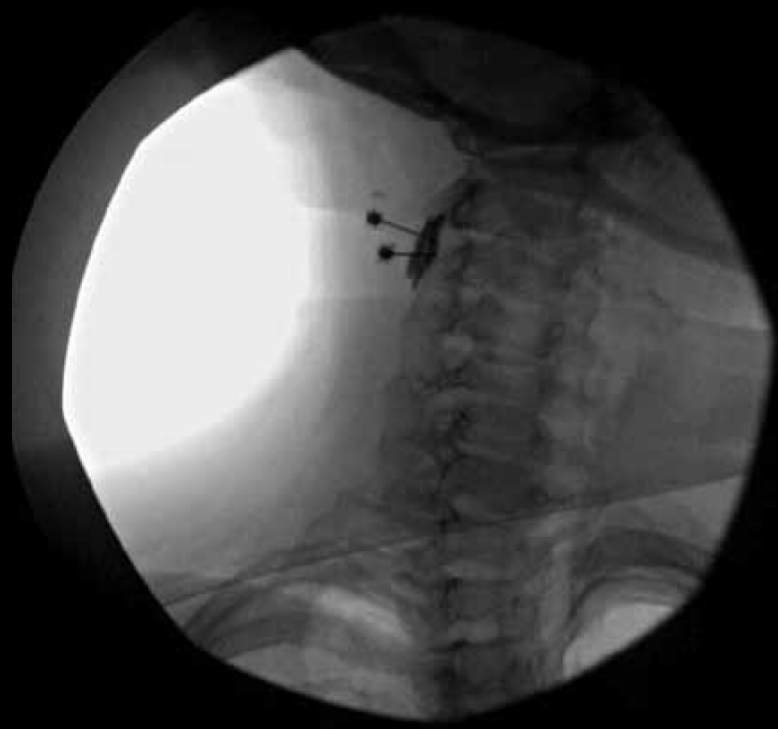


- Target sites for RF therapies:
  - (a) dorsal root entry zone,
  - (b) dorsal root ganglion,
  - (c) medial branch of dorsal ramus,
  - (d) peripheral nerves,
  - (e) sympathetic ganglia



- C2-C3 junction and upper 1/3 of C3 waist. AP view of fluoroscopic image with the placement of the needle

Interventional Options for Cervicogenic Headaches
Neuromodulation

Neurostimulation for Refractory Cervicogenic Headache: A Three-Year Retrospective Study

Marzieh Eghtesadi, MD*; Elizabeth Leroux, MD†; Marie-Pierre Fournier-Gosselin, MD‡; Paul Lespérance, MD§; Luc Marchand, MD†; Heather Pim, MD¶; Andreea Adelina Artenie, MSc**; Line Beaudet, PhD††; Guy Pierre Boudreau, MD‡‡

Neuromodulation. 2018 Apr;21(3):302-309.

- **Objective**: assess the efficacy and safety of **unilateral occipital nerve** stimulation in patients suffering from refractory cervicogenic headaches
- Retrospective chart review of **16 patients** with daily moderate to severe cervicogenic headaches for a median of 15 years
- **Results**:
  - **1 year follow-up**: 69% of patients were responders; median of 40 point improvement in VAS (p=0.0013); clinically significant improvement in anxiety and depression in 60% of patients
  - **3 year follow-up**: 38% of patients were responders; median of 15 point improvement in VAS (p=0.019); clinically significant improvement in anxiety and depression in 23-34% of patients

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Neuromodulation. 2018 Apr;21(3):302-309.

Table 3. Change from baseline at one-year follow-up.

Variable	Baseline	One-year follow-up	*p* value*
VAS score, median (Q1–Q3)			
Overall (*n* = 16)	40.0 (30.0–60.0)	80.0 (60.0–90.0)	0.0013
Responders (*n* = 11)	40.0 (35.0–55.5)	80.0 (80.0–90.0)	
Non-responders (*n* = 5)	40.0 (30.0–60.0)	60.0 (55.0–60.0)	
HIT6 score, median (Q1–Q3)			
Overall (*n* = 16)	67.0 (66.0–74.5)	49.5 (40.0–57.3)	0.0005
Responders (*n* = 11)	66.0 (66.0–75.0)	46.0 (39.0–52.0)	
Non-responders (*n* = 5)	67.0 (67.0–74.0)	61.0 (52.0–63.0)	
HADS-A (positive), *n* (%)			
Overall (*n* = 16)	10 (62.5%)	4 (25.0%)	0.0391
Responders (*n* = 11)	8 (72.7%)	2 (18.2%)	
Non-responders (*n* = 5)	2 (40.0%)	2 (40.0%)	
HADS-D (positive), *n* (%)			
Overall (*n* = 16)	10 (62.5%)	4 (25.0%)	0.0156
Responders (*n* = 11)	8 (72.7%)	3 (27.3%)	
Non-responders (*n* = 5)	2 (40.0%)	1 (20.0%)	
On disability leave because of headache			
Overall (*n* = 7)	7 (100%)	3 (42.9%)	
Responders (*n* = 3)	3 (100%)	1 (33.3%)	
Non-responders (*n* = 4)	4 (100%)	2 (50.0%)	

Neurostimulation for Refractory Cervicogenic Headache: A Three-Year Retrospective Study

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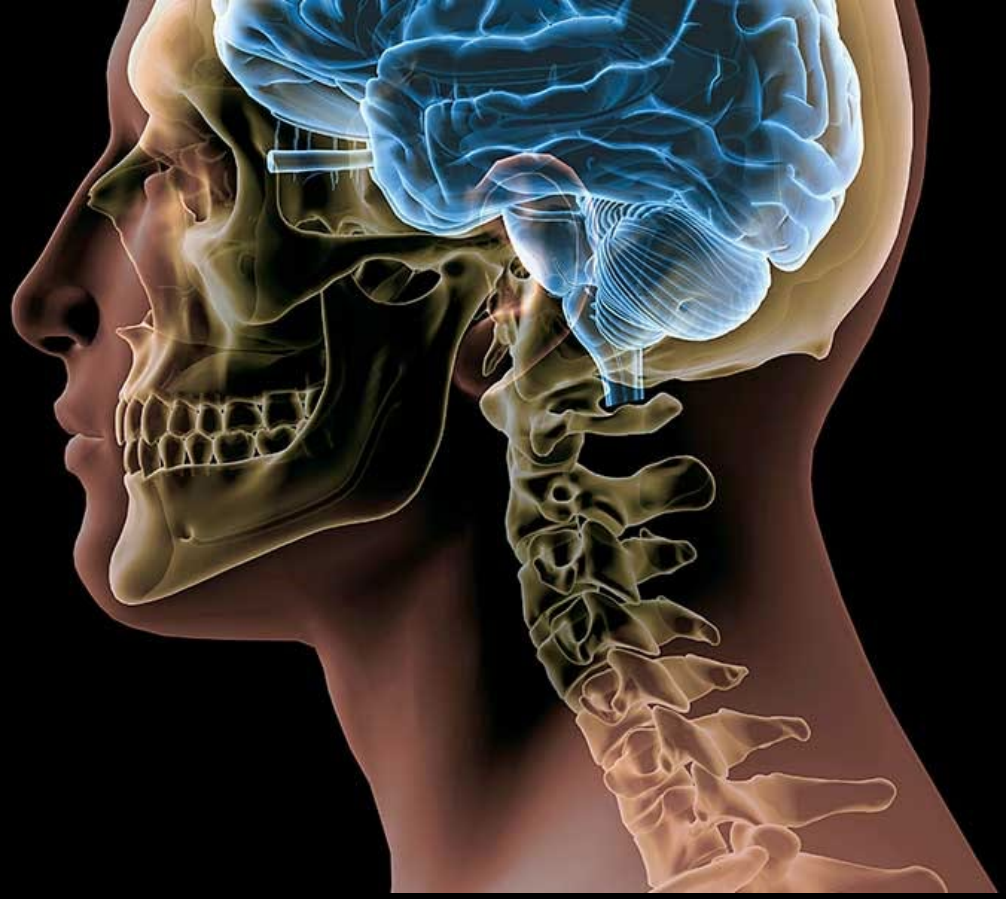
Neuromodulation. 2018 Apr;21(3):302-309.

Table 4. Change from baseline at three-year follow-up.

Variable	Baseline	Three-year follow-up	*p* value*
VAS score, median (Q1–Q3)			
Overall (*n* = 16)	40.0 (30.0–60.0)	65.0 (48.8–75.0)	0.019
Responders (*n* = 6)	40.0 (22.5–50.0)	57.5 (50.0–76.3)	
Non-responders (*n* = 10)	40.0 (40.0–60.0)	65.0 (48.8–72.5)	
HIT6 score, median (Q1-Q3)			
Overall (*n* = 16)	67.0 (66.0–74.5)	59.5 (49.0–66.0)	0.0017
Responders (*n* = 6)	76.0 (68.5–76.0)	55.5 (51.3–66.5)	
Non-responders (*n* = 10)	66.5 (66.0–68.5)	63.5 (47.8–65.8)	
HADS-A (positive), *n* (%)			
Overall (*n* = 16)	10 (62.5%)	6 (40.0%)†	0.2188†
Responders (*n* = 6)	6 (100.0%)	4 (80.0%)†	
Non-responders (*n* = 10)	4 (40.0%)	2 (20.0%)	
HADS-D (positive), *n* (%)			
Overall (*n* = 16)	10 (62.5%)	4 (28.6%)‡	0.1250‡
Responders (*n* = 6)	4 (66.7%)	2 (40.0%)†	
Non-responders (*n* = 10)	6 (60.0%)	2 (22.2%)†	
Work disability status because of headache			
Overall (*n* = 7)	7 (100%)	2 (28.6%)	
Responders (*n* = 2)	2 (100%)	1(50.0%)	
Non-responders (*n* = 5)	5 (100%)	2 (40.0%%)	



Interventional Options for Cervicogenic Headaches
Various Other Techniques

PAINWEEK®

The Feasibility and Efficacy of Ultrasound-Guided C2 Nerve Root Coblation for Cervicogenic Headache

Baishan Wu, MD,* Li Yue, MD,† Fenglong Sun, MD,‡ Shan Gao, MD,§ Bing Liang, MD,¶ and Tao Tao, MD‖,‖

Pain Medicine, 20(6), 2019, 1219–1226

- Objective: retrospective study into the feasibility and efficacy of **ultrasound-guided C2 nerve root coblation** in managing 26 patients with cervicogenic headache
- **Results**:
  - **100% of patients had >50% pain relief one day** after coblation
  - **92% had a decrease in their pain score of 50% or more at 24-week** follow-up
  - Mean pain score was 7.38 ± 1.13 before coblation and 1.85 ± 0.83 one day after coblation (P<0.001)
  - At 12 and 24 weeks after coblation, the mean pain scores were 2.96 ± 0.96 (P<0.001) and 3.08 ± 1.38 (P<0.008), respectively

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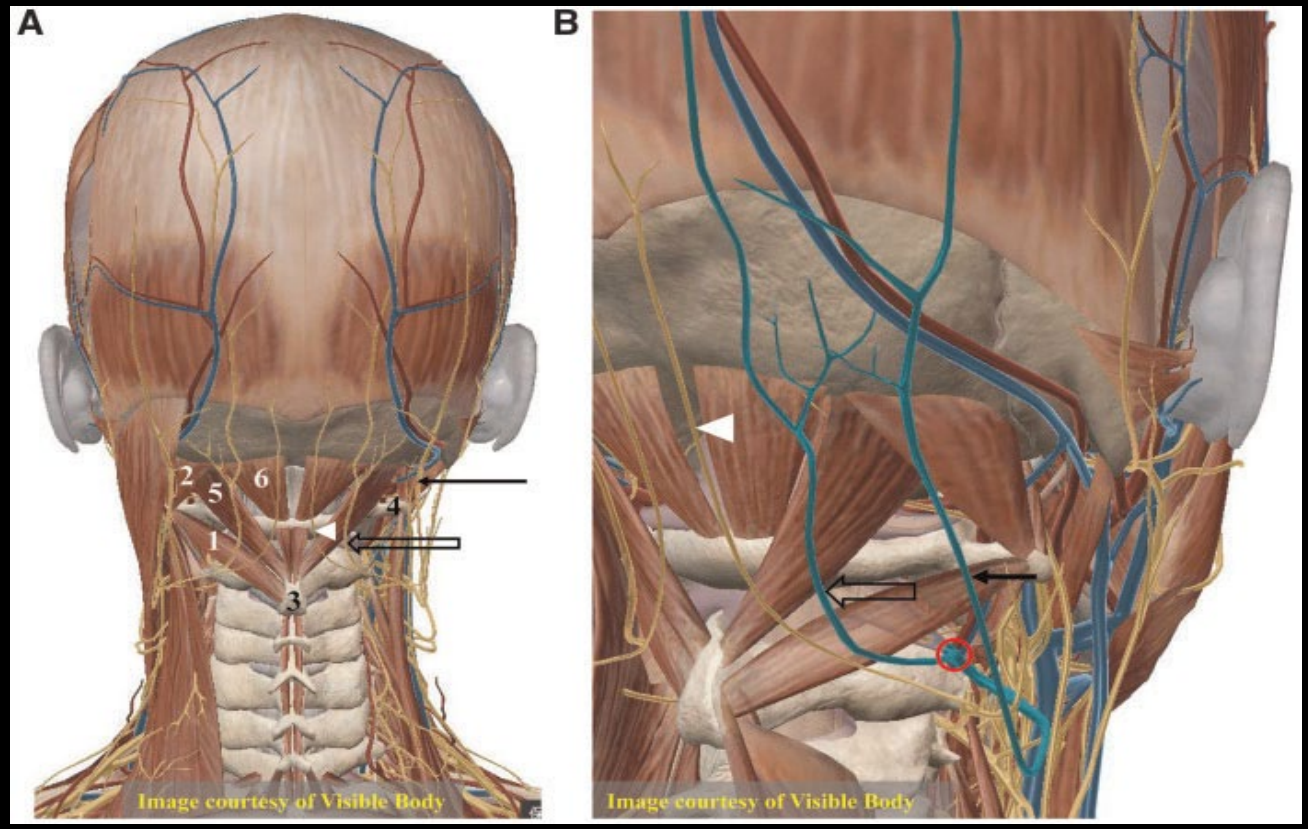
- **Virtual anatomical structure of the oblique capitis inferior (OCI) and C2 cervical nerve.**
  - A. Coronal view of the OCI and ventral ramus of the C2 cervical nerve
  - B. Virtual anatomical structure of coblation target
- 1) OCI
- 2) Oblique capitis superior [OCS]
- 3) C2 spinous process
- 4) C1 transverse process
- 5) Musculi rectus capitis posterior major
- 6) Musculi rectus capitis posterior minor
- **Arrow**: lesser occipital nerve (LON; minor occipital nerve)
- **Hollow arrow**: greater occipital nerve (GON; major occipital nerve)
- **Arrow head**: tertiary occipital nerve. Red circle: C2 cervical root (coblation target)



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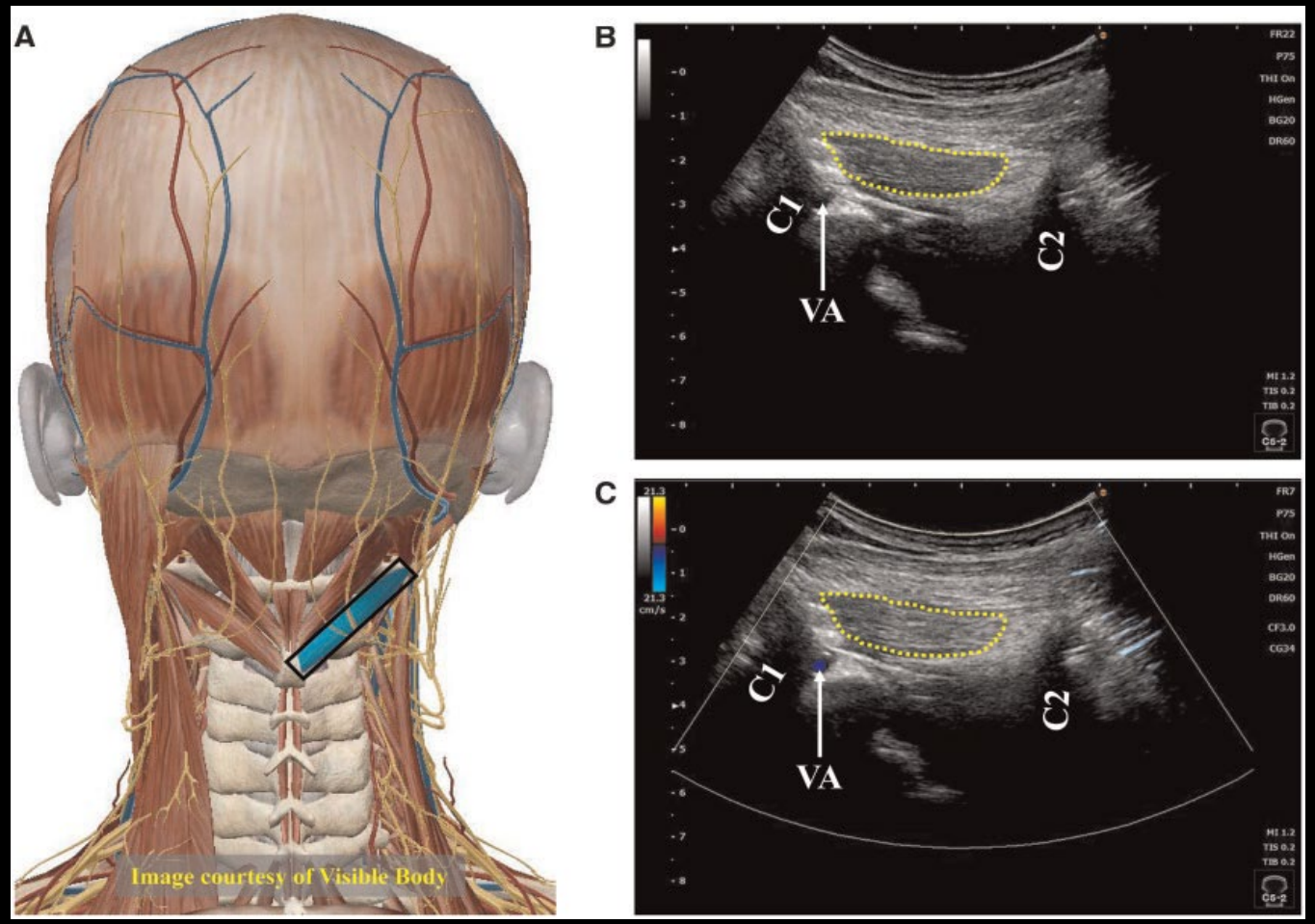
- **Ultrasound scanning plane and image of oblique capitis inferior**
  - **A)** Virtual ultrasound scanning plane and ultrasound probe position
  - **B, C)** Ultrasound image of oblique capitis inferior
  - **Black rectangle**: ultrasound scanning plane
  - **Yellow dotted contour**: oblique capitis inferior
  - **C1** = C1 transverse process;
  - **C2** = C2 spinous process;
  - **VA** = vertebral artery



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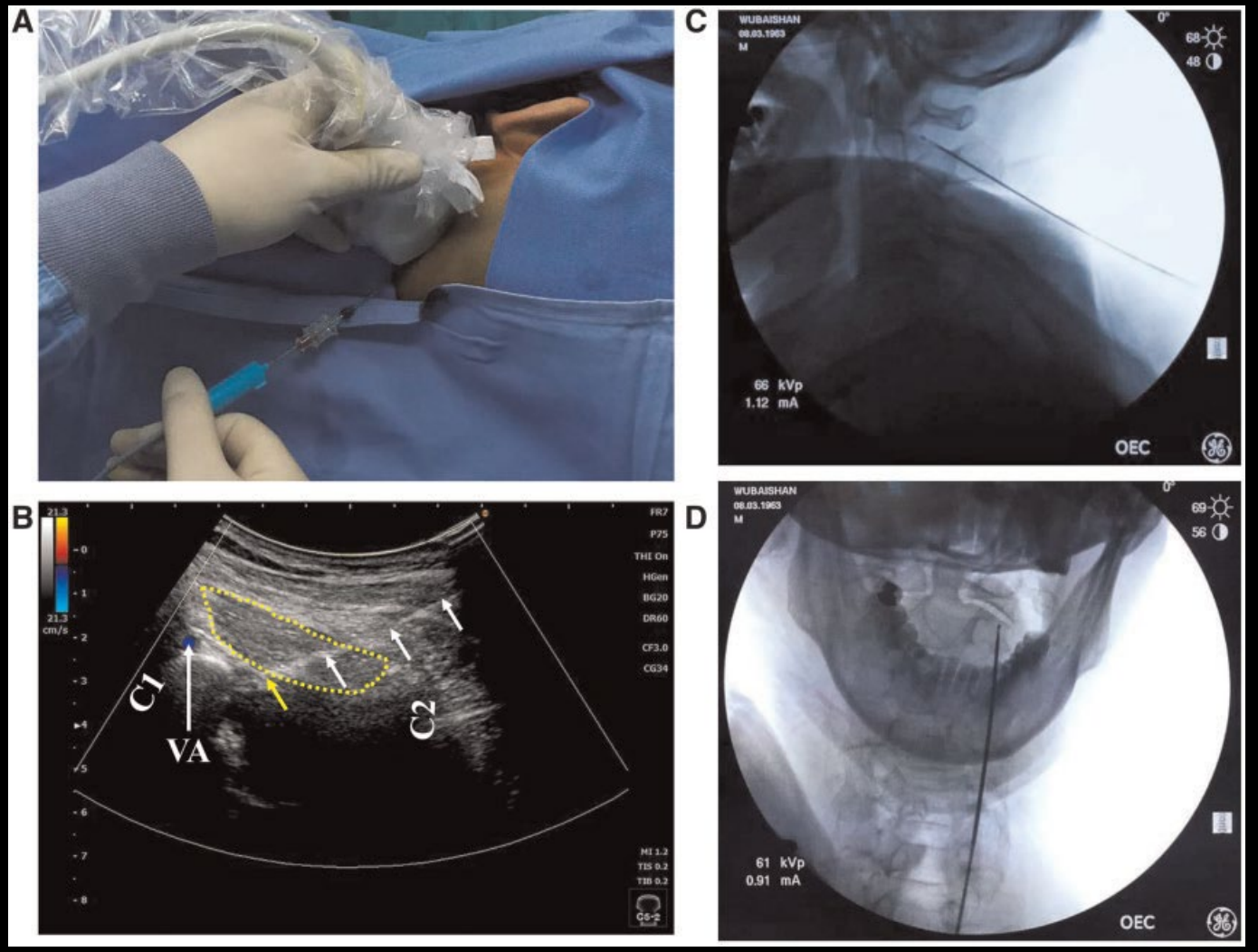
- **Ultrasound-guided coblation through oblique capitis inferior**
  - **A)** Patient's position and coblation needle insertion
  - **B)** Ultrasound image of the oblique capitis inferior (OCI) and coblation needle
  - **C, D)** Needle tip position confirmed by fluoroscopy (anterior/ posterior [open mouth] and lateral position)
  - **White arrow**: needle
  - **Yellow arrow**: needle tip
  - **Yellow dotted contour**: OCI
  - **C1** = C1 transverse process;
  - **C2** = C2 spinous process;
  - **VA** = vertebral artery



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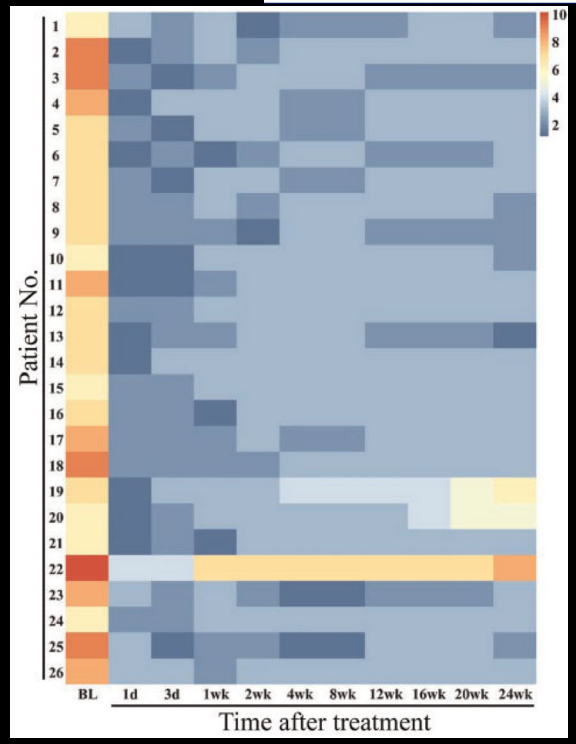

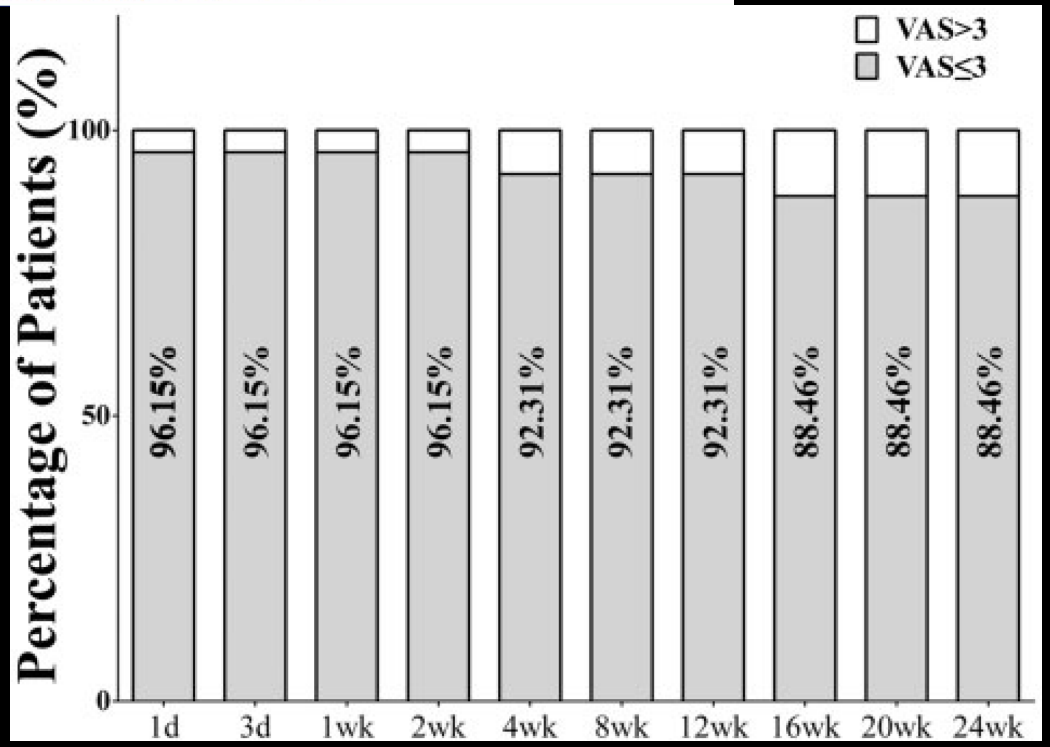

- **Heatmap of pain intensity (VAS).** The heatmap indicates the raw VAS of each patient during 24 weeks of follow-up after coblation treatment

- **Mild pain percentage at different follow-up time points**. The grey part represents the mild pain percentage of patients (VAS ≤ 3) at different follow-up time points, and the white part represents the moderate or more intense pain percentage of patients at different follow-up time points

Sissel Breivold Roland, Are Hugo Pripp, Mbachi Ruth Msomphora and Gunnvald Kvarstein*

The efficacy of botulinum toxin A treatment for tension-type or cervicogenic headache: a systematic review and meta-analysis of randomized, placebo-controlled trials

Scand J Pain 2021; aop

- **Botulinum toxin A** (BONTA) inhibits the release of acetylcholine at the neuromuscular junction and inhibits contraction of skeletal muscles. If the headache pain is precipitated by increased tone in cervical muscles, local injections of BONTA could represent a **prophylactic measure**

- **Systematic review + meta analysis** of 12 RCTs on tension-type headaches and **4 RCTs on cervicogenic headaches**

- Results: Majority of the trials found **no significant difference** on the primary outcome measure for BONTA treatment compared with placebo. 3 “positive” trials, reporting significant difference in favor of BONTA treatment, but 2 of these were hampered by low validity and quality scores and high risk of bias

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The efficacy of botulinum toxin A treatment for tension-type or cervicogenic headache: a systematic review and meta-analysis of randomized, placebo-controlled trials

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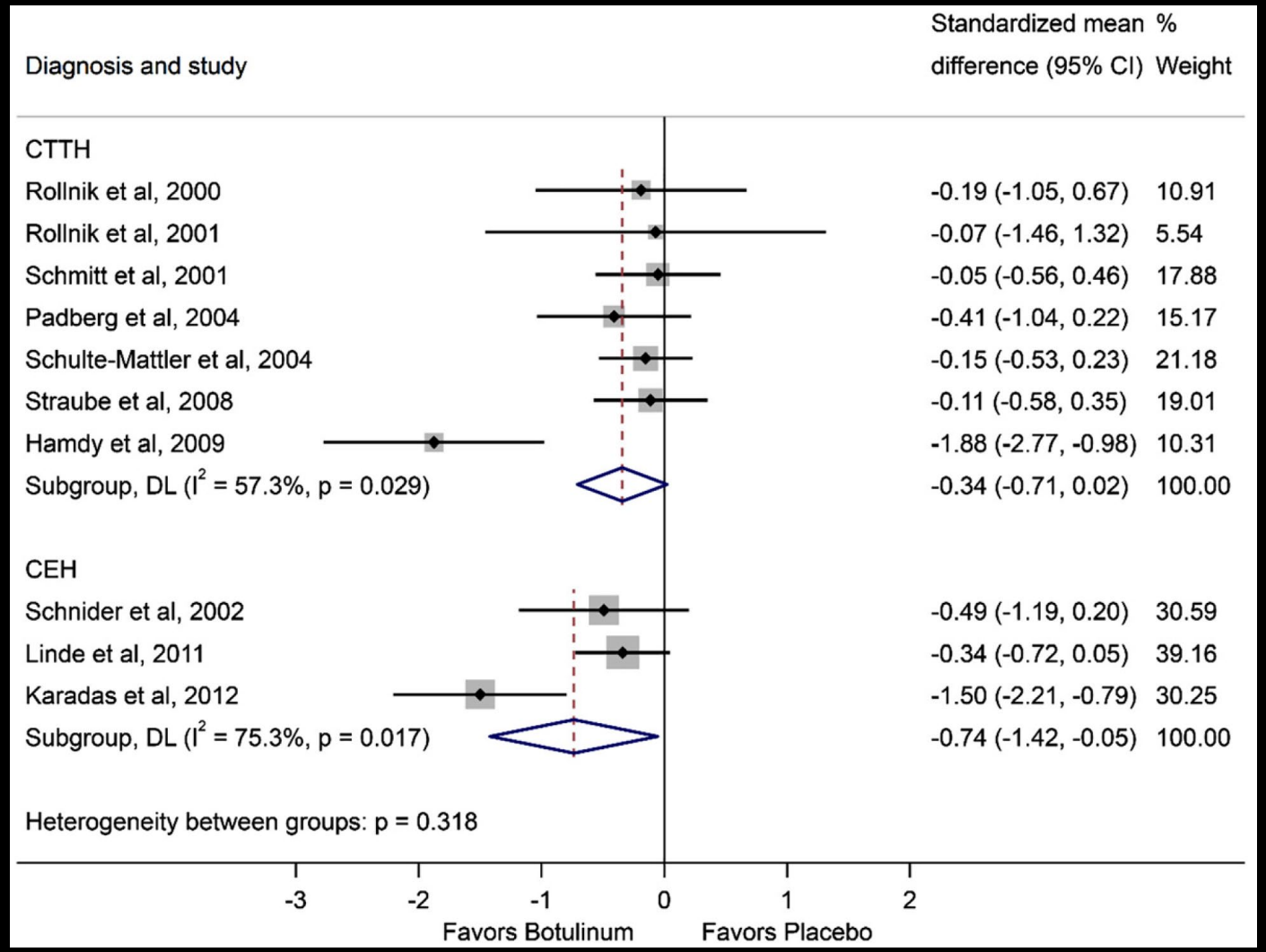
- Standardized mean difference in **headache frequency** between botulinum toxin A vs placebo



PAINWEEK

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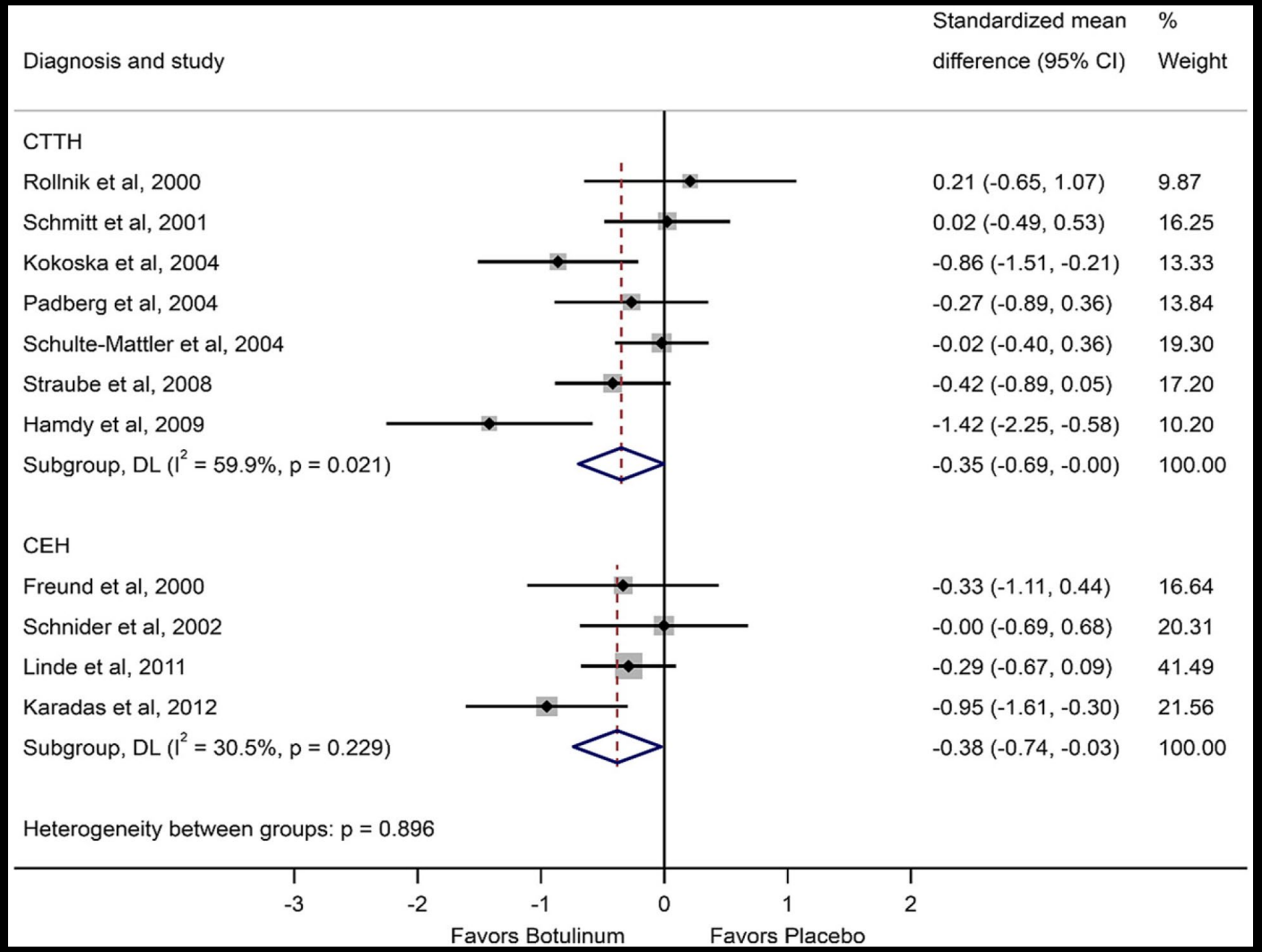


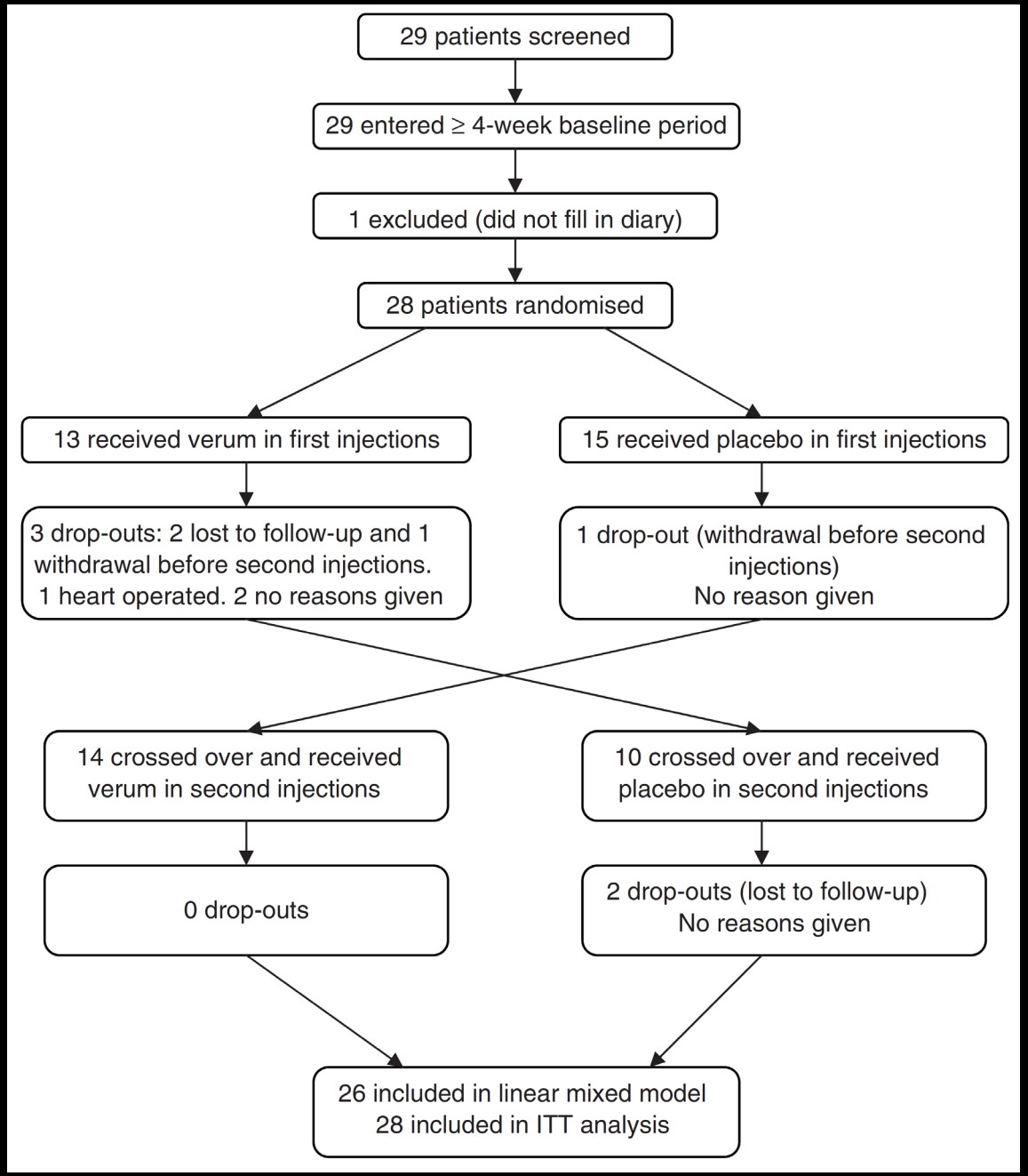
PainWeek

Onabotulinum toxin A treatment of cervicogenic headache: A randomised, double-blind, placebo-controlled crossover study Cephalalgia. 2011 May;31(7):797-807.

Mattias Linde[1,2], Knut Hagen[1,2], Øyvind Salvesen[1], Gøril Bruvik Gravdahl[2], Grethe Helde[1] and Lars Jacob Stovner[1,2]

- Preliminary reports regarding injections in the neck of onabotulinum toxin A have been positive in cervicogenic headache (CeH). The aim was to perform the first methodologically rigorous trial

- **n = 28 patients**; **injections of either onabotulinum toxin A or placebo** were given in fixed sites in the neck muscles on the pain side



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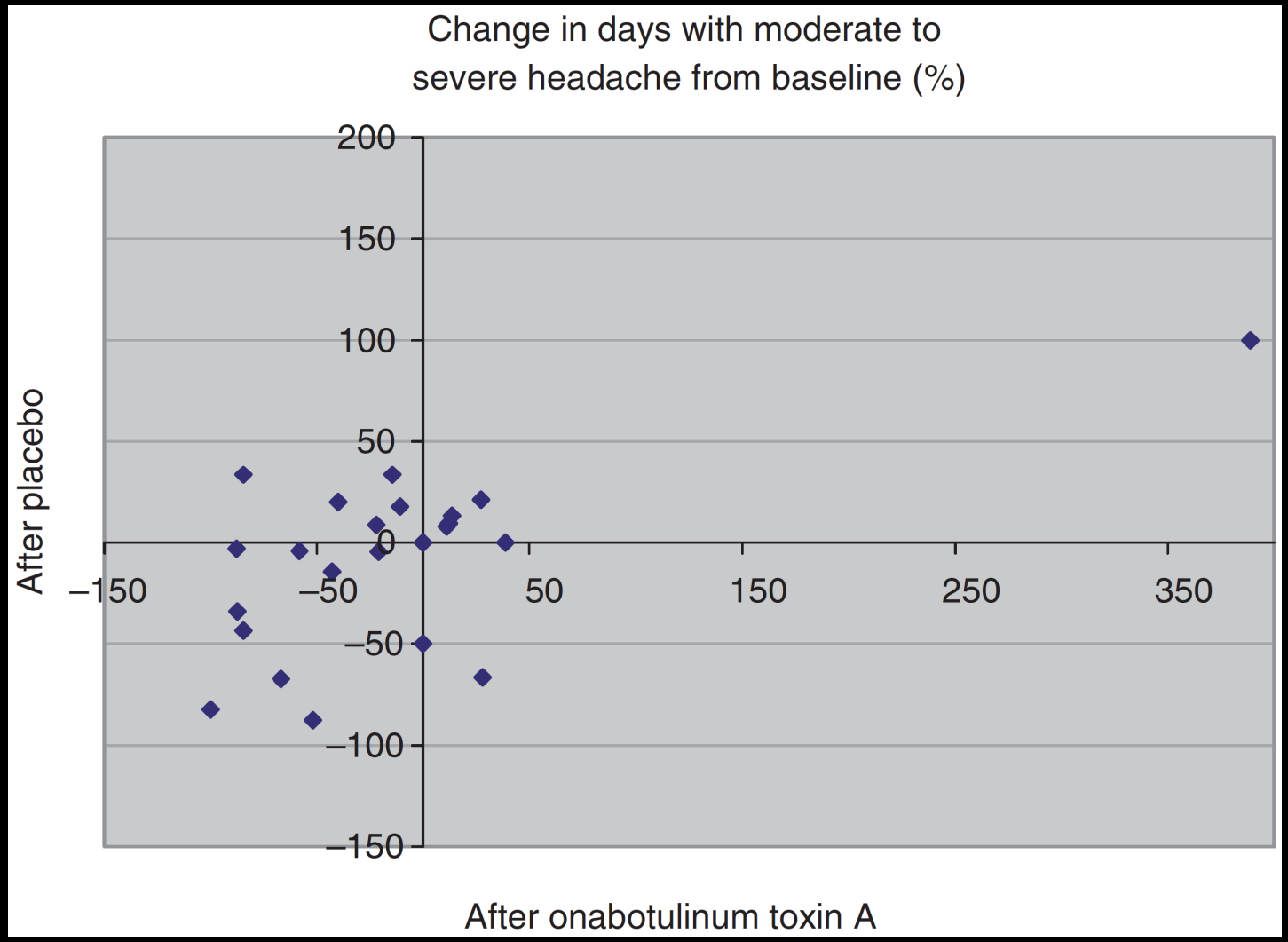

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- Results:
  - **No significant difference between verum and placebo** (p = 0.084) with regard to the primary endpoint (reduction of days with moderate to severe headache)
  - Side-effects of onabotulinum toxin A were minor and short-lasting

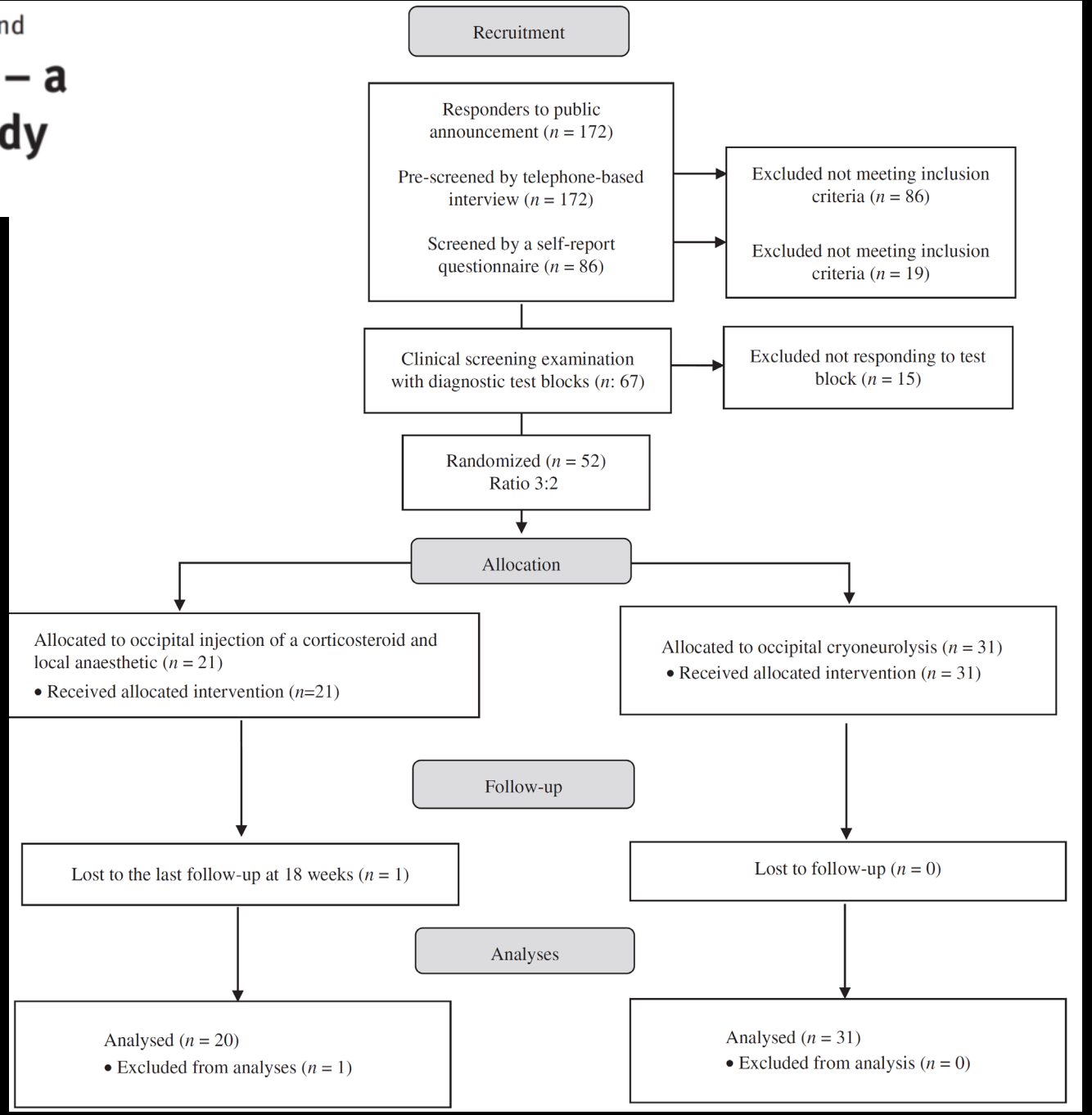
Variable	Mean value during baseline ± 1 SD	Mean difference after onabotulinum toxin A* (95% CI)	Mean difference after placebo* (95% CI)	Significance (*p*, mixed linear model)
Frequency of moderate to severe headache (days/week)	4.5 ± 0.4	−0.7 (−1.1; −0.3)	−0.4 (−0.8; 0.0)	$p = 0.084$
Mean intensity of headache (scale 1–3)	2.0 ± 0.1	−0.4 (−0.2; 0.1)	−0.2 (−0.3; 0.0)	$p = 0.14$
Headache frequency (days/week)	6.4 ± 0.3	−0.6 (−1.0; −0.3)	−0.5 (−0.8; −0.1)	$p > 0.20$
Headache index (headache intensity × headache frequency)	13.0 ± 1.1	−0.9 (−2.0; 0.2)	−1.3 (−2.5; −0.2)	$p > 0.20$
Neck pain frequency (days/week)	5.7 ± 0.4	0.1 (−0.3; 0.4)	0.1 (−0.3; 0.5)	$p > 0.20$
Duration of pain in head and/or neck (hours/week)	86.0 ± 8.1	2.0 (−2.8; 6.9)	−2.4 (−7.5; 2.6)	$p = 0.054$
Analgesic use (doses/week)	12.6 ± 2.5	−2.9 (−5.1; −0.7)	−4.0 (−6.4; −1.7)	$p > 0.20$
Sick leave (days/week)	0.5 ± 0.4	0.5 (0.2; 0.8)	−0.1 (−0.4; 0.2)	$p < 0.001$

Gunnvald Kvarstein*, Henrik Högström, Sara Maria Allen and Jan Henrik Rosland

Cryoneurolysis for cervicogenic headache – a double blinded randomized controlled study

Scand J Pain. 2019 Dec 18;20(1):39-50.

- **Aim**: assess the clinical efficacy of a cryoneurolysis compared to corticosteroid combined with a local anesthetic
- **Study**: randomized, double blinded, comparative study with an 18-week follow-up
- **n = 31** patients received occipital cryoneurolysis; **n = 21** patients received injection of methylprednisolone + bupivacaine



Gunnvald Kvarstein*, Henrik Högström, Sara Maria Allen and Jan Henrik Rosland

Cryoneurolysis for cervicogenic headache – a double blinded randomized controlled study

Scand J Pain. 2019 Dec 18;20(1):39-50.

- **Results**:
  - **Significant pain reduction >50% in both treatment groups**, slightly improved neck function and reduced number of opioid consumers
  - Pain intensity increased gradually after 6-7 weeks, but did not reach baseline within 18 weeks
  - **After 18 weeks**, 29% rated the headache as much improved, and 24% as somewhat improved, but a large proportion **(78%) reported need for further intervention/treatment**

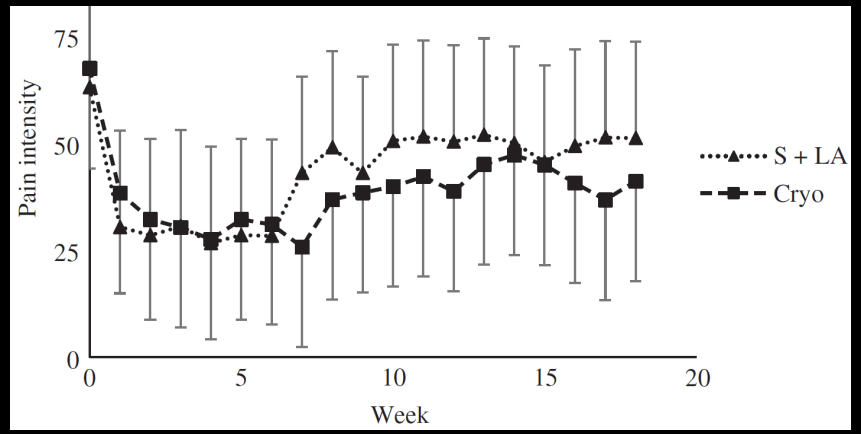


Table 2: Maximum headache intensity before and after treatment (*n*: 52).

Issue	Baseline		Week 1		CI	*p*-Value	Week 6		CI	*p*-Value	Week 18		CI	*p*-Value
	Mean	SD	Mean	SD			Mean	SD			Mean	SD		
Whole sample	66	21	35	24		<0.001[a]	30	22		<0.001[a]	45	33		<0.001[a]
S+LA	63	23	31	21	−18.6 to 7.9	0.42[b]	28	20	−13.3 to 11.4	0.88[b]	51	35	−7.2 to 30.2	0.22[b]
Cryo	68	23	38	21			31	20			41	35		

Gunnvald Kvarstein*, Henrik Högström, Sara Maria Allen and Jan Henrik Rosland

Cryoneurolysis for cervicogenic headache – a double blinded randomized controlled study

Scand J Pain. 2019 Dec 18;20(1):39-50.

Table 3: Group comparisons on number of responders to treatment (*n*: 50).

Issue	Week 1			Week 6			Week 18		
	S+LA	Cryo	*p*-Value	S+LA	Cryo	*p*-Value	S+LA	Cryo	*p*-Value
Pain reduction		*n* (%)			*n* (%)			*n* (%)	
>30%	13 (62)	18 (62)	0.99	12 (57)	22 (76)	0.16	9 (47)	12 (46)	0.94
>50%	12 (57)	14 (48)	0.54	10 (48)	17 (59)	0.44	8 (42)	9 (35)	0.61

Table 4: Patients' impression of change after 18 weeks (*n*: 51).

Issue	Much improved		Moderately improved		Unchanged		Moderately worse		Much worse	
	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo
										n (%)
Global status	7 (44)	16 (62)	5 (31)	3 (12)	10 (24)	6 (20)	0 (0)	0 (0)	0 (0)	1 (4)
Headache intensity	5 (25)	10 (32)	5 (25)	7 (23)	10 (50)	14 (45)	0 (0)	0 (0)	0 (0)	0 (0)
Neck movement	3 (14)	4 (13)	3 (14)	5 (16)	14 (67)	20 (65)	0 (0)	1 (3)	0 (0)	1 (3)

Conclusions

- **Interventional pain modalities for refractory migraines** include neurostimulation (stimulation targeting the peripheral or trigeminal nerves, transcranial magnetic stimulation, and remote electrical neuromodulation), nerve blocks (targeting the occipital nerve or the sphenopalatine ganglion), steroid injections and pulsed RF

- **Interventional pain modalities for cervicogenic headaches** include RFA, neurostimulation, ESI, cryoneurolysis, occipital nerve blocks, lateral atlantoaxial joint intra-articular injections, and C2 nerve root coblation

- Interventional treatment options that **target the inhibition of painful nerves constitute a promising avenue for patients with refractory headache** disorders, and large RCT are needed to clearly demonstrate their efficacy


Thank You!
nick.knezevic@gmail.com